RESEARCH ARTICLE

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Effect of Abaloparatide on Bone Microarchitecture Assessed by Trabecular Bone Score in Women With Osteoporosis: Post Hoc Analysis of ACTIVE and ACTIVExtend

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ABSTRACT

Although bone mineral density (BMD) is a predictor of fracture, many fractures occur in women with *T*-scores > −2.5. Bone microarchitecture, assessed by trabecular bone score (TBS), predicts fracture risk independent of BMD. We evaluated whether abaloparatide improves TBS and whether TBS trends were associated with vertebral fracture risk reduction. Women with osteoporosis randomized to abaloparatide or placebo for 18 months (ACTIVE), followed by alendronate for 24 months (ACTIVExtend), with evaluable TBS, were included in this post hoc analysis ($N = 911$). TBS was calculated from spine BMD scans using an algorithm adjusted for tissue thickness (TBS_{th}) at baseline, 6, 18, and 43 months. Mean increments in TBS_{th} from baseline within and between treatment groups, proportion of women with TBS_{th} increments above least significant change (LSC) and proportion with degraded TBS_{th} (<1.027) were calculated. Risk estimates for vertebral fracture were compared using binary logistic regressions adjusted for baseline age and spine BMD. At baseline, 42% had degraded TBS_{th}. Mean TBS_{th} increased 4% after 18 months abaloparatide ($p < 0.001$) and was unchanged with placebo. After 2 subsequent years of alendronate, the total cumulative TBS_{th} increase was 4.4% with abaloparatide/alendronate and 1.7% with placebo/alendronate (group difference, $p < 0.001$). At 43 months, the proportion of women with degraded TBS_{th} had declined to 21% with abaloparatide/alendronate and 37% with placebo/alendronate ($p < 0.05$). An increase in $TBS_{th} \geq$ LSC was observed in 50% of abaloparatide-treated women at 18 months and was associated with decreased odds (odds ratio [OR]; 95% confidence interval [CI]) of vertebral fracture (0.19; 95% CI, 0.04–0.80, 6 months; 0.30; 95% CI, 0.11–0.79, 43 months). In conclusion, abaloparatide increased TBS_{th} rapidly and progressively over 18 months and increments were maintained over 2 years with alendronate. TBS_{th} increase was associated with vertebral fracture risk reduction. Microarchitectural improvement may be one mechanism by which abaloparatide strengthens vertebral bone. © 2023 Radius Health, Inc and The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: ANALYSIS/QUANTITATION OF BONE; DXA; CLINICAL TRIALS; OSTEOPOROSIS; ANABOLICS

Introduction

Osteoporosis and associated fractures lead to decreased quality of life, increased mortality, and increased healthcare costs, representing a substantial personal and public health burden.[1-3] Despite the availability of multiple diagnostic tools and treatments, many women do not receive a diagnosis of osteoporosis or appropriate treatment.[4,5]

Bone mineral density (BMD) assessed from dual-energy X-ray absorptiometry (DXA) scans, the most widely used screening and diagnostic tool, is an important predictor of fracture.[6] However, many fractures occur in women with *T*-scores above osteoporosis range, suggesting that other skeletal factors contribute to fracture risk.[7,8] Bone microarchitecture, distinct from BMD, is reported to have a substantial influence on bone strength and fracture risk.[7,9-13] Trabecular bone score (TBS) is a gray-level

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textural analysis of the two-dimensional (2D) DXA images (or other X-ray image modalities) of the lumbar spine (or femur) that are routinely obtained during BMD testing. TBS is an independent predictor of fracture risk[7,14] widely used in clinical practice and present in many clinical guidelines. TBS provides a reliable noninvasive surrogate assessor of bone microarchitecture that correlates well with three-dimensional (3D) bone microarchitectural parameters as measured by bone histomorphometry and/or micro-computed tomography (μCT).[7,10,15,16] Regional soft tissue presence can impact X-ray absorption and eventually affect TBS estimates. Previous TBS algorithms have adjusted for body mass index (BMI) as a surrogate for soft tissue thickness.[16] The most recent TBS algorithm addresses this issue by directly accounting for the regional soft tissue thickness instead of the usual BMI as a surrogate.[17]

Abaloparatide is an anabolic treatment for osteoporosis that is an analog of parathyroid hormone-related peptide (PTHrP). Abaloparatide selectively binds the PTH type-1 receptor and favors bone formation.[18,19] In a phase 2 study, abaloparatide improved trabecular microarchitecture at 12 and 24 weeks in the lumbar spine as indicated by a significant increase in TBS relative to baseline and placebo.[20] In the pivotal ACTIVE trial (Clinicaltrials.gov identifier NCT01343004), 18 months of abaloparatide treatment significantly increased BMD at the lumbar spine and total hip and significantly reduced the risk of vertebral and nonvertebral fractures compared with placebo.[19] In the ACTIVExtend trial (Clinicaltrials.gov identifier NCT01657162), eligible patients were treated with alendronate for an additional 24 months.[21] Patients treated with abaloparatide followed by alendronate had further increases in BMD and sustained fracture risk reduction compared to patients who received placebo followed by alendronate.

The aim of this retrospective analysis was to evaluate TBS in participants from the ACTIVE and ACTIVExtend trials to determine whether mean TBS improved with abaloparatide, what proportion of women would attain a significant above least significant change (LSC), whether the proportion of degraded TBS decreased with abaloparatide, and whether TBS improvements persisted during subsequent alendronate treatment. In addition, we aimed to determine if there was an association between TBS improvements and vertebral fracture risk reduction.

Patients and Methods

Study design

Women who completed the ACTIVE and ACTIVExtend trials and had evaluable TBS at baseline, 6, 18, and 43 months were included in this retrospective analysis. Women for whom information about vertebral fractures was not available, who had fewer than two evaluable vertebrae by DXA, or who had TBS values meeting Rosner's test for outliers were excluded from the analysis.[22] To assess longitudinal changes, pairs of scans from patients that were identified as potential outliers underwent visual assessment for potential artifacts. Each pair of scans was examined by two independent reviewers in a blinded fashion. In cases of disagreement, an adjudicator was utilized. The most frequent reason for exclusion from our analysis was due to inconsistent artifactual soft tissue effects on the image (especially on low-energy images where darker zones related to gaz-induced abnormal values) between visits for a given patient. If a significant difference in regional pixel intensities (due to artifactual soft tissue) was present in one of the two images, it was excluded. Artifactual images at baseline were excluded from further analysis; artifactual images in postbaseline time points were excluded from the analysis including the respective time point. As a result, 24 patients were excluded from all visits. In addition, three, nine, and four patients were excluded from 6-month, 18-month, and 43-month TBS changes, respectively. Because the number of outliers was <5% of the total sample, the mean and confidence interval (CI) differences with and without outliers (Fig. 1, Fig. S1) were minor. The inclusion or

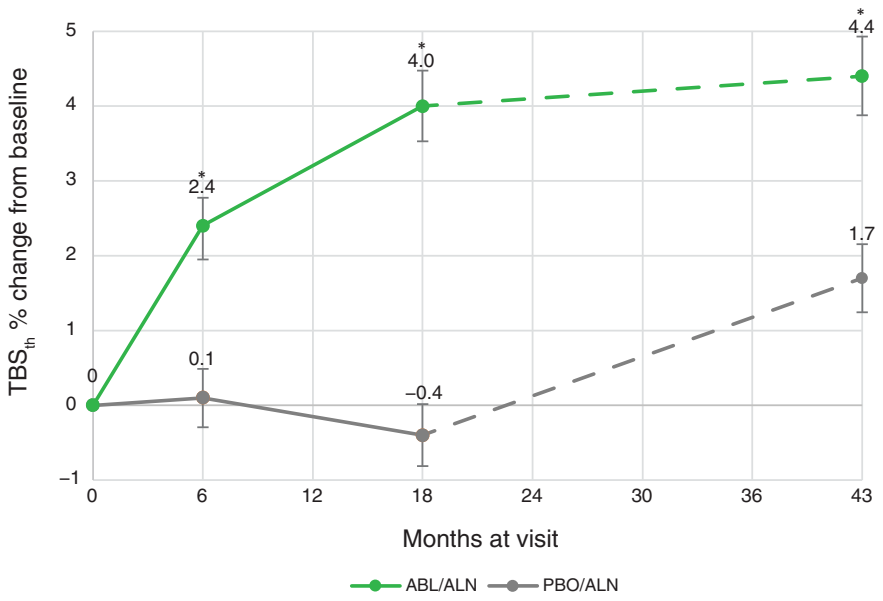

Fig. 1. Mean TBS_{th} (95% CI) percent change over time. *$p < 0.001$. Both ABL and PBO ended at 18 months (solid lines); at 19 months, all subjects started ALN for 24 months (dotted lines). ABL, abaloparatide; ALN, alendronate; CI, confidence interval; PBO, placebo; TBS_{th}, trabecular bone score adjusted for tissue thickness.

exclusion of the outliers would not have changed the study conclusions.

The study designs for ACTIVE and ACTIVExtend have been previously described in detail (Fig. S2).[19,21] Briefly, women in the ACTIVE trial were randomized 1:1:1 to receive 18 months of blinded treatment with once-daily subcutaneous 80 μg abaloparatide or matching placebo, or open-label, once-daily subcutaneous 20 μg teriparatide. Women in the abaloparatide or placebo groups who completed ACTIVE without experiencing any treatment-related serious adverse events (SAEs) were eligible to enroll in ACTIVExtend where all women received open-label therapy with alendronate 70 mg orally once weekly for 24 months. Women assigned to the teriparatide group did not enter the extension study and were not considered for these analyses.

The ACTIVE and ACTIVExtend trial protocols were approved by the ethics committee at every participating institution and were conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent to participate in both studies.

Outcome assessments

TBS was calculated from spine DXA scans at baseline, 6, 18, and 43 months using an updated algorithm (TBS iNsights prereleased v.4.0; Medimaps Group SA, Geneva, Switzerland) that provides TBS corrected for soft tissue based on abdominal tissue thickness (TBS_{th}). The TBS calculation was performed centrally but blinded from clinical outcomes and treatment assignment.

TBS_{th} thresholds used in this study were the corresponding values to the TBS_{BMI} thresholds (tertiles) reported by McCloskey and colleagues,[16] to which the known offset between the patented algorithms was applied. As in McCloskey and colleagues,[16] we refer to TBS values lower than 1.027 as corresponding to degraded microarchitecture, between 1.027 and 1.074 as moderately degraded microarchitecture, and higher than 1.074 as normal microarchitecture.

Vertebral fractures were assessed using the method of Genant and colleagues[23] as described.[19] Briefly, radiologists (Bioclinica-Synarc) graded each woman's vertebrae, with a decrease in height of 20% to 25% defined as mild, 26% to 40% as moderate, and more than 40% as severe. All radiographs in which an incident fracture was identified were confirmed by a second radiologist, and a third radiologist adjudicated the incident fracture, if necessary. All treatments were blinded from radiologists and adjudicators.

Statistical analyses

All inferential testing was two-tailed, with $p < 0.05$ set as the threshold for statistical significance. IBM SPSS statistical software (version 26.0; IBM Corp., Armonk, NY, USA) was used for all statistics.

TBS_{th} change from baseline was calculated and mean increments in TBS_{th} were compared within each group at 6, 18, and 43 months compared to baseline and between groups at each time point. Differences between treatment groups were assessed by percent change from baseline and using generalized estimating equation models with adjustments for treatment group, visit, visit and treatment interaction, age, and BMI. LSC is the extent of change above which a difference in measurement could be presumed clinically real and not secondary to precision errors with a confidence level of 95%. The 2019 ISCD Official Positions statement strictly advises the reporting of LSC in a patient's follow-up DXA report and comments on the lack of clinical meaning if the percent change in measurement is not significant based on the LSC.[24] In the current analysis, LSC was calculated following the approach used in Bilezikian and colleagues.[20] In this similar randomized controlled trial (RCT) analysis, the mean precision error of 1.53% was used as a mean of several prior studies (range, 1.12%–2.1%). The TBS_{th} precision error reported by the manufacturer is 10% to 15% better than the precision error for TBS_{BMI}. Based on this, 1.33% was considered an adequate precision error for TBS_{th} for this analysis. Subsequently, the LSC would be 3.75%. The proportion of women with degraded TBS_{th} was calculated for each visit and compared between groups.

The incidence of vertebral fractures at 43 months was calculated for each study group (placebo and abaloparatide) and as a function of TBS_{th} percent change ≥LSC (+3.75%) at 6 months. Binary logistic regressions adjusted for age and lumbar spine BMD at baseline were used to study the odds ratio (OR) of having a vertebral fracture in groups that had TBS_{th} changes ≥LSC value compared with those with TBS_{th} changes <LSC.

Results

Baseline characteristics

A total of 911 women who completed ACTIVE and ACTIVExtend had evaluable TBS_{th} and were included in this post hoc analysis: 457 in the abaloparatide/alendronate group and 454 in the placebo/alendronate group (Fig. S3). Baseline characteristics in the subgroup of patients included in this analysis were similar in the two groups (Table 1) and similar to those in the full ACTIVE and ACTIVExtend study populations. In the abaloparatide/alendronate group, 185 of 457 (40%) women and 194 of 454 (43%) in the placebo/alendronate group had degraded TBS_{th} at baseline with no significant group differences.

Changes in TBS_{th} during ACTIVE and ACTIVExtend

In patients treated with abaloparatide in ACTIVE, TBS_{th} increased from baseline by 2.4% at 6 months and 4.0% at 18 months (Fig. 1). There was no significant change in TBS_{th} from baseline in the placebo group at 6 months (0.1%) or 18 months (−0.4%). The group difference for abaloparatide compared with placebo was significant at both 6 and 18 months ($p < 0.001$).

After 2 years of treatment with alendronate in the ACTIVExtend trial, TBS_{th} increased an additional 0.4% in the abaloparatide/alendronate group and 2.1% in the placebo/alendronate group (difference, $p = 0.02$). The total cumulative increase from baseline was 4.4% with abaloparatide/alendronate and 1.7% with placebo/alendronate (43-month group difference, $p < 0.001$). The TBS_{th} increase as compared to baseline remained significant after adjusting for age, TBS_{th}, and BMI at baseline. Results were also similar for the sensitivity analysis without exclusion of outliers (Fig. S3).

At 6 and 18 months, 37% and 50% of women treated with abaloparatide had increased TBS_{th} ≥ LSC compared with 21% and 16%, respectively, for placebo (Table 2). At 43 months, 52% of women in the abaloparatide/alendronate group had increased TBS_{th} ≥ LSC compared with 32% in the placebo/alendronate group.

Table 1. Baseline Characteristics of Study Population

Characteristic	ABL/ALN ($n = 457$)	PBO/ALN ($n = 454$)
Age (years), mean ± SD	68.7 ± 6.4	68.7 ± 6.1
Weight (kg), mean ± SD	61.1 ± 9.8	60.7 ± 9.9
Height (cm), mean ± SD	156.4 ± 7.1	156.4 ± 7.2
BMD T-score, mean ± SD		
Lumbar spine	−2.84 ± 0.89	−2.84 ± 0.93
Femoral neck	−2.18 ± 0.65	−2.21 ± 0.70
Total hip	−1.88 ± 0.72	−1.93 ± 0.75
TBS_{th} (unitless), mean ± SD	1.045 ± 0.078	1.035 ± 0.083
TBS_{th}, *n* (%)		
Normal or partially degraded	272 (60)	260 (57)
Degraded	185 (40)	194 (43)
TBS_{BMI} (unitless), mean ± SD	1.253 ± 0.093	1.251 ± 0.094
TBS_{BMI}, *n* (%)		
Normal or partially degraded	283 (62)	284 (63)
Degraded	174 (38)	170 (37)

Abbreviations: ABL, abaloparatide; ALN, alendronate; BMD, bone mineral density; PBO, placebo; SD, standard deviation; TBS_{BMI}, trabecular bone score adjusted for body mass index; TBS_{th}, trabecular bone score adjusted for tissue thickness.

The proportion of women in the abaloparatide group with degraded TBS_{th} decreased from 40% at baseline to 30% at 6 months and to 24% at 18 months (trend, $p < 0.001$). The percentage of women with degraded TBS_{th} decreased further with alendronate, and, by 43 months, only 21% of women in the abaloparatide/alendronate group had degraded TBS_{th}. In comparison, the proportion of women in the placebo group with degraded TBS_{th} did not change over 18 months. At 43 months, after 2 years of alendronate following placebo, the percentage of women with degraded TBS_{th} decreased modestly to 37% (Fig. 2).

Changes in TBS_{th} and vertebral fracture risk

After 43 months of treatment, four of 455 (0.9%) women in the abaloparatide/alendronate group and 23 of 453 (5.1%) women in the placebo/alendronate group had a vertebral fracture (Table 3). All four women in the abaloparatide/alendronate group who sustained a vertebral fracture had TBS_{th} < LSC at 6 months and three of four had TBS_{th} < LSC at 43 months. In the placebo/alendronate group, 21 of the 23 women with a vertebral fracture at 43 months had TBS_{th} < LSC at 6 months (21/359 [5.8%] TBS_{th} < LSC versus 2/93 [2.2%] TBS_{th} ≥ LSC) and 19 of 23 at 43 months (19/309 [6.1%] TBS_{th} < LSC versus 4/144 [2.8%] TBS_{th} ≥ LSC). In the overall study population, the OR (95% CI) of having a vertebral fracture at 43 months with TBS_{th} change ≥LSC compared with <LSC between 0 and 6 months and 0 and 43 months were 0.19 (0.04–0.80) and 0.30 (0.11–0.79), respectively. The OR (95% CI) of having a vertebral fracture in women with degraded TBS_{th} at baseline whose TBS_{th} remained degraded at 43 months compared with those whose

Table 2. Percentage of Patients With TBS_{th} Increased ≥LSC and Decreased <LSC

	TBS_{th} increased ≥LSC (+3.75)		TBS_{th} decreased <LSC (−3.75)	
Parameter	ABL/ALN ($n = 457$)	PBO/ALN ($n = 454$)	ABL/ALN ($n = 457$)	PBO/ALN ($n = 454$)
0–6 months, *n* (%)	171 (37%)	93 (21%)	45 (10%)	89 (20%)
0–18 months, *n* (%)	227 (50%)	73 (16%)	26 (6%)	98 (22%)
0–43 months, *n* (%)	235 (52%)	144 (32%)	32 (7%)	56 (12%)

Abbreviations: ABL, abaloparatide; ALN, alendronate; LSC, least significant change; PBO, placebo; TBS_{th}, trabecular bone score adjusted for tissue thickness.

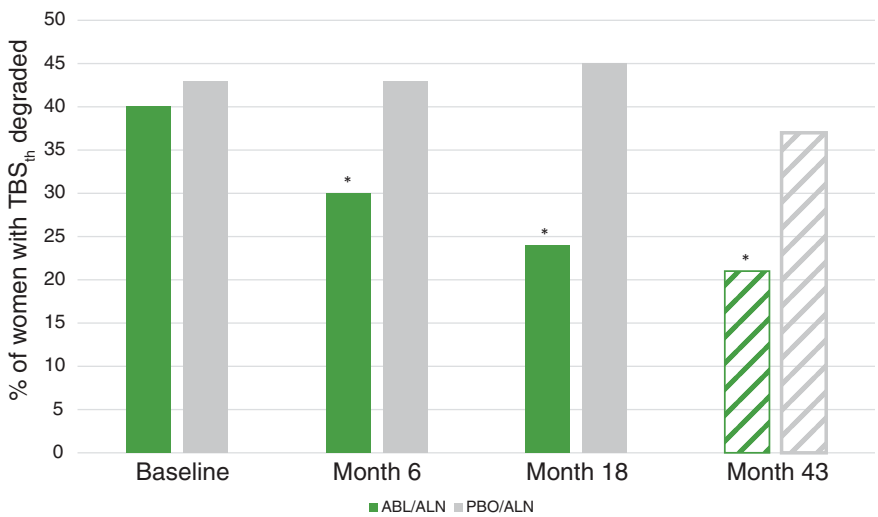

Fig. 2. Percent TBS_{th} degraded over time. *$p < 0.05$. Both ABL and PBO ended at 18 months (solid bars); at 19 months, all subjects started ALN for 24 months (striped bars). ABL, abaloparatide; ALN, alendronate; PBO, placebo; TBS_{th}, trabecular bone score adjusted for tissue thickness.

Table 3. Incidence of Vertebral Fracture by TBS_{th} Changes Over 43 Months

	ABL/ALN	PBO/ALN	Overall
% Change TBS_{th} at 6 months, *n/N* (%)			
TBS_{th} ≥ LSC	0/171 (0)	2/93 (2.2)	2/264 (0.8)
TBS_{th} < LSC	4/284 (1.4)	21/359 (5.8)	25/643 (3.9)
Total	4/455 (0.9)	23/452 (5.1)	27/907 (3.0)
% Change TBS_{th} at 43 months, *n/N* (%)			
TBS_{th} ≥ LSC	1/235 (0.4)	4/144 (2.8)	5/379 (1.3)
TBS_{th} < LSC	3/220 (1.4)	19/309 (6.1)	22/529 (4.2)
Total	4/455 (0.9)	23/453 (5.1)	27/908 (3.0)

ABL, abaloparatide; ALN, alendronate; LSC, least significant change; PBO, placebo; TBS_{th}, trabecular bone score adjusted for tissue thickness.

TBS_{th} moved out of the degraded category at 43 months was 2.88 (0.61–13.58).

Discussion

In this post hoc analysis of ACTIVE and ACTIVExtend, bone microarchitecture, as assessed by TBS_{th}, improved significantly with abaloparatide followed by alendronate. The largest increase in TBS_{th} was observed in the first 6 months of abaloparatide treatment but further gains were observed from 6 to 18 months, and the increase in TBS_{th} was maintained during 24 months of alendronate treatment. Mean TBS_{th} gain with 2 years of alendronate (after placebo; 2.1%) was half that seen with 18 months of abaloparatide (4%). Abaloparatide followed by alendronate resulted in a statistically significant 50% decline in the proportion of women with degraded TBS_{th}, whereas treatment with alendronate alone reduced this percentage by less than 20% (nonsignificant). The likelihood of having a new vertebral fracture was lower in women who had increases in TBS_{th} beyond LSC.

Studies with other medications to treat osteoporosis have also demonstrated positive effects on TBS. In a study by Tsai and colleagues,[25] 24 months of teriparatide monotherapy increased TBS by 2.7% from baseline, whereas the antiresorptive agent denosumab increased TBS by 1.8%, and combination therapy with teriparatide plus denosumab resulted in a 4.5% increase in TBS from baseline. Senn and colleagues[26] demonstrated 4.3% and 0.3% increases from baseline in TBS with 24 months teriparatide and ibandronate treatment, respectively. Other studies with bisphosphonate treatment have shown increases in TBS ranging from 0.2% per year to 1.4% over 36 months of treatment.[27,28] The increase in TBS_{th} with alendronate in our study was larger than seen with alendronate in prior studies, but the patient populations differ in age, baseline BMD, and other factors which can affect this outcome. In addition, TBS_{th} is more sensitive and has better precision error than the TBS measurement used in most prior studies. The observed changes in TBS with abaloparatide in our study are consistent with its anabolic action. In a bone histomorphometry study, 3 months of abaloparatide treatment stimulated bone formation on all four bone envelopes in the iliac crest (cancellous, endocortical, intracortical, and periosteal surfaces) and increased both remodeling-based and modeling-based bone formation.[29]

In our post hoc analysis, the number of vertebral fracture events was too low to evaluate a relationship between changes in TBS and fracture risk solely in abaloparatide-treated patients (only four vertebral fractures were seen in that group). Similarly, studies with teriparatide were not powered to assess the correlation between TBS change and fracture risk.[25] However, when analyzing the overall population, we found that the odds of having a vertebral fracture were much lower in women who had changes in TBS_{th} ≥ LSC compared to those with changes in TBS_{th} < LSC. Consistent with our findings, a number of studies have demonstrated a relationship between low TBS and increased fracture risk.[9,11-13,30] However, few studies have evaluated how treatment-related TBS changes affect fracture risk. Leslie and colleagues[31] showed that antiresorptive (more than 80% bisphosphonate) treatment-related TBS increases were not significantly related to fracture risk reduction. However, TBS increases in that study were relatively low and likely reflected maintenance, rather than improvement, of bone microstructure (consistent with the mechanism of action of bisphosphonates). Additional studies are needed to evaluate the correlation between treatment-related TBS changes and fracture risk in patients with osteoporosis in which the expected effect of a given molecule on bone microarchitecture is sufficiently high (anabolic treatment) or patients are treated sufficiently long (long-term antiresorptive treatments; eg, minimum 5 years).

Our study has some limitations. First, the number of vertebral fractures in abaloparatide-treated patients was very small; however, this is consistent with the large spine BMD gain seen with this agent and the known correlations between BMD increases and TBS improvement. In addition, this trial only included osteoporotic women, most of whom were white. The generalization of results to men or other ethnicities should be made with caution. Also, TBS_{th} thresholds used in this study were derived from an offset analysis of the classical TBS thresholds[16] and further verified on a subset of the meta-analysis. The optimal approach would be to derive the TBS_{th} thresholds from the same meta-analysis sample (ie, entire dataset). Finally, the LSC considered in this analysis was not calculated directly in the study population. It was based on LSC values reported previously in the literature and the change in precision error between TBS_{BMI} and TBS_{th} reported by their developers. Our study is limited in regard to the number of vertebral fractures (27 vertebral fractures in 911 women), thus the grouped analysis (gain or loss in significant change) adds some power.

Conclusions

Eighteen months of abaloparatide treatment improved bone microarchitecture, and the improvement in microarchitecture was twice as large with abaloparatide/alendronate compared to alendronate alone. 50% of women who were treated with abaloparatide had increases in TBS_{th} greater than or equal to the LSC at 18 months, an improvement that was associated with decreased odds of sustaining a vertebral fracture. These findings suggest that the improvement in bone microarchitecture contributes to the effect of abaloparatide on bone strength and fracture risk reduction.

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Author Contributions

Felicia Cosman: Conceptualization; investigation; project administration; supervision; visualization; writing – original draft; writing – review and editing. **Didier Hans:** Conceptualization; data curation; formal analysis; software; writing – original draft; writing – review and editing. **Enisa Shevroja:** Formal analysis; methodology; visualization; writing – review and editing. **Yamei Wang:** Formal analysis; methodology; visualization; writing – review and editing. **Bruce Mitlak:** Funding acquisition; investigation; writing – review and editing.

Conflict of Interest

FC has received institutional grants and research support from Amgen and Radius Health, Inc. (Radius); has served as a consultant for Amgen, Radius, Enterabio, Pfizer/Myovant, and Obseva; has served on the speakers' bureaus for Amgen and Radius; and has served on advisory boards for Amgen and Radius. DH is co-owner of the trabecular bone score patent and is a part-time employee of and owns company stock in Medimaps Group, which was contracted by Radius to conduct the study. Medimaps was blinded from clinical outcomes and from treatment group at the time of the central TBS analysis. ES has no conflict of interest. YW and BM are employees and shareholders of Radius.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.4764.

Data Availability Statement

Data that underlie the results reported in a published article may be requested for further research 6 months after completion of FDA or EMA regulatory review of a marketing application (if applicable) or 18 months after trial completion (whichever is latest). Radius will review requests individually to determine whether (i) the requests are legitimate and relevant and meet sound scientific research principles, and (ii) are within the scope of the participants' informed consent. Prior to making data available, requestors will be required to agree in writing to certain obligations, including without limitation, compliance with applicable privacy and other laws and regulations. Proposals should be directed to info@radiuspharm.com.

References

1. Office of the Surgeon General (US). Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD: US Dept of Health and Human Services; 2004.
2. Gold T, Williams SA, Weiss RJ, et al. Impact of fractures on quality of life in patients with osteoporosis: a US cross-sectional survey. J Drug Assess. 2019;8(1):175-183.
3. Williams SA, Daigle SG, Weiss R, Wang Y, Arora T, Curtis JR. Economic burden of osteoporosis-related fractures in the US Medicare population. Ann Pharmacother. 2021;55(7):821-829.
4. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359-2381.
5. Rodrigues AM, Eusébio M, Santos MJ, et al. The burden and undertreatment of fragility fractures among senior women. Arch Osteoporos. 2018;13(1):22.
6. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal Osteoporosis-2020 update. Endocr Pract. 2020;26(Suppl 1):1-46.
7. Harvey NC, Glüer CC, Binkley N, et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone. 2015;78:216-224.
8. Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary healthcare level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield. Available from https://frax.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf. Accessed January 17, 2023.
9. Del Rio LM, Winzenrieth R, Cormier C, Di Gregorio S. Is bone microarchitecture status of the lumbar spine assessed by TBS related to femoral neck fracture? A Spanish case-control study. Osteoporos Int. 2013;24(3):991-998.
10. Hans D, Barthe N, Boutroy S, Pothuaud L, Winzenrieth R, Krieg M-A. Correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. J Clin Densitom. 2011;14(3):302-312.
11. Krueger D, Fidler E, Libber J, Aubry-Rozier B, Hans D, Binkley N. Spine trabecular bone score subsequent to bone mineral density improves fracture discrimination in women. J Clin Densitom. 2014;17(1):60-65.
12. Leslie WD, Johansson H, Kanis JA, et al. Lumbar spine texture enhances 10-year fracture probability assessment. Osteoporos Int. 2014;25(9):2271-2277.
13. Nassar K, Paternotte S, Kolta S, Fechtenbaum J, Roux C, Briot K. Added value of trabecular bone score over bone mineral density for identification of vertebral fractures in patients with areal bone mineral density in the non-osteoporotic range. Osteoporos Int. 2014;25(1):243-249.
14. Muschitz C, Kocijan R, Haschka J, et al. TBS reflects trabecular microarchitecture in premenopausal women and men with idiopathic osteoporosis and low-traumatic fractures. Bone. 2015;79:259-266.
15. Leslie WD, Shevroja E, Johansson H, et al. Risk-equivalent T-score adjustment for using lumbar spine trabecular bone score (TBS): the Manitoba BMD registry. Osteoporos Int. 2018;29(3):751-758.
16. McCloskey EV, Odén A, Harvey NC, et al. A meta-analysis of trabecular Bone score in fracture risk prediction and its relationship to FRAX. J Bone Miner Res. 2016;31(5):940-948.
17. Shevroja E, Aubry-Rozier B, Hans G, et al. Clinical performance of the updated trabecular Bone score (TBS) algorithm, which accounts for the soft tissue thickness: the OsteoLaus study. J Bone Miner Res. 2019;34(12):2229-2237.
18. Hattersley G, Dean T, Corbin BA, Bahar H, Gardella TJ. Binding selectivity of Abaloparatide for PTH-Type-1-receptor conformations and effects on downstream signaling. Endocrinology. 2016;157(1):141-149.
19. Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316(7):722-733.
20. Bilezikian JP, Hattersley G, Fitzpatrick LA, et al. Abaloparatide-SC improves trabecular microarchitecture as assessed by trabecular bone score (TBS): a 24-week randomized clinical trial. Osteoporos Int. 2018;29(2):323-328.
21. Bone HG, Cosman F, Miller PD, et al. ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. J Clin Endocrinol Metab. 2018;103(8):2949-2957.
22. Rosner's Test for Outliers. Accessed April 14, 2022. Available from: https://search.r-project.org/CRAN/refmans/EnvStats/html/rosnerTest.html.

23. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993; 8(9):1137-1148.
24. 2019 ISCD Official Positions. Adult. Available from: https://iscd.org/wp-content/uploads/2021/09/2019-Official-Positions-Adult-1.pdf. Accessed July 29, 2022.
25. Tsai JN, Jiang LA, Lee H, Hans D, Leder BZ. Effects of teriparatide, denosumab, or both on spine trabecular microarchitecture in DATA-switch: a randomized controlled trial. J Clin Densitom. 2017;20(4):507-512.
26. Senn C, Günther B, Popp AW, Perrelet R, Hans D, Lippuner K. Comparative effects of teriparatide and ibandronate on spine bone mineral density (BMD) and microarchitecture (TBS) in postmenopausal women with osteoporosis: a 2-year open-label study. Osteoporos Int. 2014;25(7):1945-1951.
27. Krieg MA, Aubry-Rozier B, Hans D, Leslie WD. Manitoba Bone density program. Effects of anti-resorptive agents on trabecular bone score (TBS) in older women. Osteoporos Int. 2013;24(3):1073-1078.
28. Popp AW, Guler S, Lamy O, et al. Effects of zoledronate versus placebo on spine bone mineral density and microarchitecture assessed by the trabecular bone score in postmenopausal women with osteoporosis: a three-year study. J Bone Miner Res. 2013;28(3):449-454.
29. Dempster DW, Zhou H, Rao SD, et al. Early effects of abaloparatide on bone formation and resorption indices in postmenopausal women with osteoporosis. J Bone Miner Res. 2021;36(4): 644-653.
30. Hans D, Goertzen AL, Krieg M-A, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res. 2011;26(11):2762-2769.
31. Leslie WD, Majumdar SR, Morin SN, Hans D, Lix LM. Change in trabecular Bone score (TBS) with antiresorptive therapy does not predict fracture in women: the Manitoba BMD cohort. J Bone Miner Res. 2017;32(3):618-623.