



# Abaloparatide-SC improves trabecular microarchitecture as assessed by trabecular bone score (TBS): a 24-week randomized clinical trial

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## Abstract

**Summary** In a phase 2 trial of 222 postmenopausal women with osteoporosis aged 55 to 85 years randomized to one of three different doses of abaloparatide-SC, subcutaneous teriparatide, or placebo for 24 weeks, abaloparatide-SC resulted in improvements in skeletal microarchitecture as measured by the trabecular bone score.

**Introduction** Subcutaneous abaloparatide (abaloparatide-SC) increases total hip and lumbar spine bone mineral density and reduces vertebral and non-vertebral fractures. In this study, we analyzed the extent to which abaloparatide-SC improves skeletal microarchitecture, assessed indirectly by trabecular bone score (TBS).

**Methods** This is a post hoc analysis of a phase 2 trial of 222 postmenopausal women with osteoporosis aged 55 to 85 years randomized to abaloparatide-SC (20, 40, or 80 µg), subcutaneous teriparatide (20 µg), or placebo for 24 weeks. TBS was measured from lumbar spine dual X-ray absorptiometry (DXA) images in 138 women for whom the DXA device

was TBS software compatible. Assessments were made at baseline, 12 and 24 weeks. Between-group differences were assessed by generalized estimating equations adjusted for relevant baseline characteristics, and a pre-determined least significant change analysis was performed.

**Results** After 24 weeks, TBS increased significantly by 2.27, 3.14, and 4.21% versus baseline in participants on 20, 40, and 80 µg abaloparatide-SC daily, respectively, and by 2.21% in those on teriparatide ( $p < 0.05$  for each). The TBS in the placebo group declined by 1.08%. The TBS increase in each treatment group was significantly higher than placebo at 24 weeks ( $p < 0.0001$  for each) after adjustment for age, BMI, and baseline TBS. A dose-response was observed at 24 weeks across the three doses of abaloparatide-SC and placebo ( $p = 0.02$ ). The increase in TBS in the abaloparatide-SC 80 µg group was significantly greater than TPTD ( $p < 0.03$ ).  
**Conclusions** These results are consistent with an effect of abaloparatide-SC to improve lumbar spine skeletal microarchitecture, as assessed by TBS.

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## Introduction

Abaloparatide, a novel 34-amino acid peptide designed to be a selective activator of the PTH1 receptor signaling pathway, is a promising therapeutic approach to the treatment of osteoporosis. Abaloparatide binds selectively to the RG versus R<sup>0</sup> conformation of the PTH1 receptor, resulting in transient receptor signaling consistent with a net anabolic effect [1]. The results of the phase 3 ACTIVE trial of abaloparatide for subcutaneous injection (abaloparatide-SC) demonstrated efficacy in reducing vertebral and non-vertebral fracture incidence [2].

We hypothesized that since abaloparatide-SC is an activator of the PTH1 receptor, it is likely that its efficacy is related to improved bone microarchitecture and strength, as has been shown for teriparatide [3, 4]. To this point, animal studies with abaloparatide-SC have documented complete reversal of bone loss in ovariectomy-induced osteopenic rats and monkeys [1, 5, 6]. In monkeys, abaloparatide-SC augments not only bone mass and volume, but also bone microarchitecture and bone strength [7]. In both animal models, the increased bone formation occurs in the absence of a corresponding increase in bone resorption, resulting in marked gains in bone mass and strength [7, 8]. To date, however, the effects of abaloparatide-SC on trabecular microarchitecture and bone strength have not been assessed in human subjects.

The trabecular bone score (TBS) is a non-invasive imaging technology that takes advantage of the DXA lumbar spine image, providing skeletal information not captured by standard bone mineral density (BMD) assessments. It is a gray-level textural analysis that utilizes experimental variograms to assess 2D projection images from the DXA scan [9]. A semi-quantitative measurement, TBS is strongly correlated with a number of microarchitectural parameters that reflect bone strength [10]. A high TBS reflects better microarchitecture; whereas, a low TBS reflects worse microarchitecture [11]. In a recent meta-analysis, TBS was demonstrated to be a significant predictor of fracture risk independent of Fracture Risk Assessment Tool (FRAX)-calculated 10-year fracture risk estimate [12].

The primary objective of this study was to utilize TBS in a six-month clinical trial of several different doses of abaloparatide-SC, a single dose of teriparatide, or placebo [13], to determine the extent to which abaloparatide-SC improves skeletal microarchitecture.

## Methods

This study is a post hoc retrospective analysis of a phase 2, multicenter, international, and double-blind placebo-controlled trial conducted at 30 study centers across four countries: the USA, Argentina, India, and the UK [13]. All patients had provided informed written consent prior to their participation, in accordance with the Declaration of Helsinki for research on human subjects.

To be eligible for inclusion in the original trial, patients had to be postmenopausal women with osteoporosis, aged 55 years old or older, and not currently on long-term treatment for osteoporosis. In addition, patients could not currently be on systemic corticosteroids and could not have any other bone or spinal disease or history of past injuries or surgeries (e.g., total hip replacement, spinal rods) that would alter BMD measurements at the lumbar spine or hip. Once screened and confirmed for eligibility, patients were randomized to one of the

following five treatment arms, with each patient self-administering a single subcutaneous injection once daily for 24 weeks of placebo; one of three different doses of abaloparatide-SC (20, 40, or 80  $\mu\text{g}$ ); and teriparatide 20  $\mu\text{g}$ . All patients also received supplemental calcium (500 to 1000 mg) and vitamin D (400 to 800 IU), in accordance with local practices. Patients and investigators remained blinded to treatment with all doses of abaloparatide-SC and placebo throughout the study. Blinding was not possible in patients randomized to receive teriparatide because the drug could be delivered only via its trademarked injection pen [13].

BMD was assessed in the lumbar spine, femoral neck, and total hip by DXA at baseline and again at 12 and 24 weeks after the initiation of treatment. DXA scans were sent to a central imaging reader (BioClinica Inc., Doylestown, PA, USA) for a quality control review, followed by analysis in accordance with each manufacturer's instructions and ISCD guidelines. The two follow-up scans on each given patient were performed on the same instrument used at baseline. Each study site performed instrument quality control assessments over time (i.e., instrument standardization and phantom calibration), which were reviewed by the central reader. Further details on the methodology of the original trial have been published [13]. All vertebrae (L1 to L4) were automatically included into the analysis (about 84% of all patients). However, individual vertebrae were excluded if fractures or degenerative changes were present, in accordance with ISCD rules for individual vertebrae exclusion (more than 1 standard deviation in T-score from the immediately adjacent vertebrae).

To be eligible for the current study, patients had to have had their initial BMD measurement on a DXA scanner compatible with TBS software. TBS was calculated retrospectively using a modified TBS Calculator (v2.2) to consider soft tissue thickness directly in the algorithm instead of BMI (Medimaps group, Plan-les-Ouates, Geneva, Switzerland), using DXA files from the original phase 2 trial. All patient identifiers were removed to maintain anonymity and to ensure blinding of the investigators to all clinical parameters and outcomes. The same region of interest as BMD was used with vertebral site exclusions as noted above. Of 222 women randomized to one of the five treatment arms, 221 received at least one dose of study medication. TBS could not be calculated in 76 patients because the DXA scanner or the acquisition mode used was incompatible with TBS software. Additional patients ( $n=4$ ) were excluded as a DXA change in software (upgrade to convert a QDR 4500 W to a Discovery W) was performed in the middle of the study without TBS cross-calibration, or the DXA displayed malfunctioning detectors ( $n=3$ ) that could have led to errors in the TBS calculations.

## Statistical analysis

The primary outcome of interest was the change in TBS in the lumbar spine relative to baseline, assessed both by percentage change from baseline and by generalized estimating equations (GEE), adjusted for TBS, BMI, and age at baseline; treatment, visit, and treatment and visit interaction; and an unstructured covariance structure. A dose-response curve was calculated for the placebo group and 20, 40, or 80 µg dose groups of abaloparatide-SC. At 24 weeks, the percentage of individuals exceeding two different levels of a priori-determined least significant change (LSC) was calculated for each group, where LSC was defined as the extent of change above which a difference in TBS could be presumed real and not secondary to precision errors. The differences in proportion of patients with an increase  $\geq$  LSC were tested using the chi-square categorical test. The published precision errors for TBS vary from 1.12 to 2.1% depending on the design of the study and machine involved. The average precision across these studies was approximately 1.53% and the corresponding LSC at 95% confidence interval was  $\pm$  4.2% [3, 11, 14, 15]. This latter value was used in this study. All inferential testing was two-tailed, with  $p \leq 0.05$  set as the threshold for statistical significance. IBM SPSS statistical software (version 21.0; SPSS, Inc.) was used for all statistics.

## Results

The 138 patients included in the final analysis were generally similar to the original study population with respect to age, BMI, and lumbar spine BMD at baseline. Patients in the five treatment groups were also similar in their demographic and clinical characteristics, including baseline lumbar spine BMD and TBS measurements (Table 1).

Figure 1 shows the change in TBS over time in patients on placebo, teriparatide, and the three different doses of abaloparatide-SC. Results are expressed as percentage change

(mean  $\pm$  standard error of the mean) from baseline at 12 and 24 weeks in lumbar spine TBS. After 12 weeks, lumbar spine TBS increased by 1.33, 1.86, 2.37, and 1.16% in the abaloparatide-SC 20 µg, abaloparatide-SC 40 µg, abaloparatide-SC 80 µg, and teriparatide groups, respectively ( $p < 0.05$  for all comparisons to baseline); whereas, there was no significant increase in the placebo group (+0.23%,  $p = 0.35$ ). After 24 weeks, TBS increased versus baseline by 2.27, 3.14, 4.21, and 2.21% in the abaloparatide-SC 20 µg, abaloparatide-SC 40 µg, abaloparatide-SC 80 µg, and teriparatide groups, respectively ( $p < 0.05$  for all comparisons to baseline); while, there was a non-significant decrease in the placebo group ( $-1.08%$ ,  $p = 0.13$ ).

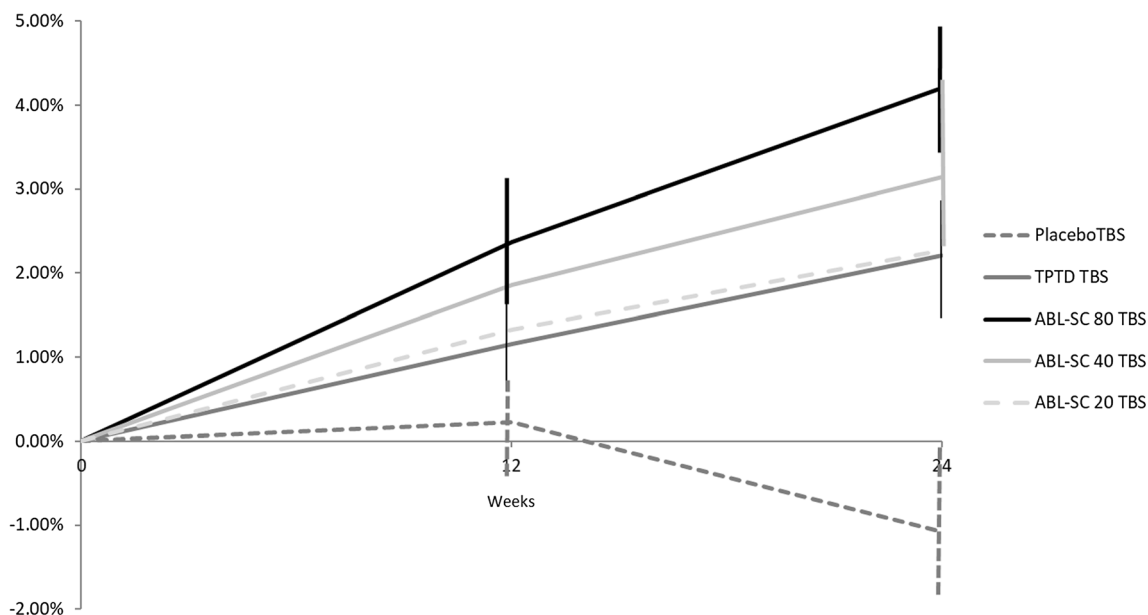
GEE analysis, adjusted for treatment group, visit, treatment group and visit interaction, TBS at baseline, age at baseline, and BMI at baseline, showed that TBS at 12 weeks increased significantly versus placebo in patients in the abaloparatide-SC 40 µg (1.61%,  $p = 0.03$ ) and 80 µg (2.07%,  $p = 0.02$ ) groups, but not in the abaloparatide-SC 20 µg (1.10%,  $p = 0.15$ ) or teriparatide (1.00%,  $p = 0.21$ ) groups. No significant differences were observed between teriparatide and the abaloparatide-SC 20 µg (0.08%,  $p = 0.91$ ), abaloparatide-SC 40 µg (0.59%,  $p = 0.42$ ) or abaloparatide-SC 80 µg (1.02%,  $p = 0.24$ ) groups.

At 24 weeks, all treated groups displayed significant TBS improvements versus placebo. TBS increased by 3.25% ( $p < 0.001$ ) in the abaloparatide-SC 20 µg group, 4.17% ( $p < 0.001$ ) in the abaloparatide-SC 40 µg group, 5.23% ( $p < 0.001$ ) in the abaloparatide-SC 80 µg group, and 3.27% ( $p = 0.002$ ) in the teriparatide group. TBS also increased significantly more in patients treated with abaloparatide-SC 80 µg (1.90%,  $p = 0.04$ ), but not in those treated with abaloparatide-SC 20 µg (0.06%,  $p = 0.95$ ) or abaloparatide-SC 40 µg (0.86%,  $p = 0.40$ ) groups compared to those treated with teriparatide. Additionally, a positive dose-response was observed at 24 weeks (least square regression  $\pm$  standard error =  $0.03 \pm 0.01$ ;  $p = 0.02$ ) when comparing the three different doses of abaloparatide-SC and placebo.

**Table 1** Baseline characteristics of the five treatment groups expressed as mean  $\pm$  SD. No significant differences were found among groups for each reported parameter

	ABL-SC 80 µg <i>n</i> = 24		ABL-SC 40 µg <i>n</i> = 25		ABL-SC 20 µg <i>n</i> = 29		TPTD <i>n</i> = 31		Placebo <i>n</i> = 29	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	64.3	6.9	65.4	6.9	68.1	6.3	66.2	7.3	66.7	7.6
BMI (kg/m <sup>2</sup> )	25.6	3.4	26.1	3.9	26.4	2.7	26.7	3.1	25.5	3.3
Lumbar spine BMD (g/cm <sup>2</sup> )	0.765	0.111	0.752	0.080	0.767	0.103	0.762	0.096	0.796	0.102
Lumbar spine TBS	1.181	0.078	1.188	0.762	1.189	0.063	1.201	0.068	1.196	0.067

ABL-SC abaloparatide-SC, BMD bone mineral density, BMI body mass index, TBS trabecular bone score, TPTD teriparatide



**Fig. 1** Comparing change in the trabecular bone score over time in patients on placebo, teriparatide, and three different doses of abaloparatide-SC (20, 40, and 80 µg). Results are expressed in percentage change (mean ± SEM) from baseline at 12 and 24 weeks in lumbar spine TBS. TBS increases from baseline were significant for

teriparatide and for all three doses of abaloparatide-SC, at 12 and 24 weeks ( $p < 0.05$  for all comparisons to baseline). For placebo, there was no significant increase at 12 weeks ( $p = 0.35$ ) and a non-significant decrease at 24 weeks ( $p = 0.13$ )

On LSC analysis (Table 2), the percentages of patients on 80 µg abaloparatide-SC daily, teriparatide 20 µg, and placebo who experienced greater than a 4.2% increase in TBS versus baseline were 52.2, 30.0, and 10.2%, respectively. No statistical difference was found between the abaloparatide-SC 80 µg and teriparatide groups ( $p = 0.12$ ) but the 80 µg abaloparatide-SC group displayed a statistically significant difference versus placebo ( $p < 0.01$ ). Differences between the teriparatide and placebo groups were not statistically significant ( $p = 0.06$ ). None of the patients in the abaloparatide-SC 80 µg group experienced a decrease in TBS versus baseline greater than the LSC, versus 6.7% of patients in the teriparatide group.

For both the teriparatide and abaloparatide-SC 80 µg groups, we calculated the number of patients exceeding the LSC for lumbar spine BMD using the same 4.2% threshold as

for TBS. In the abaloparatide-SC 80 µg group, 52 and 74% of patients exceeded the LSC for the lumbar spine TBS and BMD, respectively, and 35% of patients exceeded the LSC in both parameters. Results are 30 and 60% for teriparatide patients for lumbar spine TBS and BMD, respectively, and 27% for both parameters.

**Discussion**

Adding to the insights gained from the previously published BMD results in the same phase 2 study population [13], this analysis of the effect of abaloparatide-SC shows significant enhancement of TBS relative to placebo. Similar TBS results with teriparatide have been observed but over a longer period of time (18 to 24 months

**Table 2** Least significant change (LSC) analysis comparing abaloparatide-SC 80 µg, teriparatide (TPTD), and placebo for two different LSC levels

	LSC 95%	At 6 months		
		ABL-SC 80 µg	TPTD	Placebo
Significant individual gain (%)	+ 4.20	52.2*	30.0‡	10.3
Significant individual loss (%)	- 4.20	0.0 <sup>¥</sup>	6.7	17.2

ABL-SC abaloparatide-SC, LSC least significant change, TPTD teriparatide

\* $p = 0.001$  versus placebo

‡ $p = 0.06$  versus placebo

¥ $p = 0.05$  versus placebo



compared to 6 months here) [3]. Moreover, at both 12 and 24 weeks, the magnitude by which TBS increased was greater in the 80- $\mu\text{g}$  dose group of abaloparatide-SC (the dose that was used in the subsequent larger phase 3 trial) than in the teriparatide group. Similar results were observed for the 40- $\mu\text{g}$  abaloparatide-SC cohort. On average, in the different treatment groups, less than 10% of the variations of the BMD were explained by the variations of TBS, confirming that both parameters are unrelated, at least in part, and represent different bone properties. Also of note, an increase in TBS greater than the LSC (4.2%) was achieved by 52.2% of patients treated with abaloparatide-SC 80  $\mu\text{g}$  versus 30.0% of those treated with teriparatide. The percentage of patients on placebo exhibiting a 4.2% increase over baseline was 10.3%. It is also interesting to note that 35% of the patients treated with 80  $\mu\text{g}$  of abaloparatide increased significantly (exceeding their LSC) both their lumbar spine BMD and TBS compared to 27% for patients treated with teriparatide.

Several relatively small studies have investigated the effect of bone-active substances on TBS [16] and suggested that TBS tends to increase with treatments that increase lumbar spine BMD and to decrease without treatment. The response usually parallels the changes observed on BMD but to a lesser extent for TBS. In contrast, the magnitude of the decrease in TBS without treatment is very similar to that of BMD. It is interesting to note that there is a different TBS response depending upon the type of treatment [16]. Usually, the anti-resorptive drugs preserve bone structure, an effect supported by the mechanism of action of these agents. In these instances, monitoring TBS changes do not add substantially to what would be observed by monitoring BMD alone. However, a safety issue is relevant if TBS values were to decline significantly over time, causing concern perhaps for increased risk of fracture. In contrast, exposure to anabolic treatment is associated with an increase in TBS values above the LSC in almost two thirds of patients undergoing treatment [3]. In addition, with TBS monitoring, only 10% of patients demonstrated a decline in TBS values. In this latter case, monitoring TBS could also have clinical relevance. Whether the increase in TBS values in the context of anabolic treatment is associated with a reduction in fracture risk, over and above what an increase in BMD would indicate, remains yet to be demonstrated.

Limitations of this study include the lack of blinding of the teriparatide group. However, the TBS analysis is an objective measure and was carried out in blinded fashion without regard to the experimental arm of the study. Another limitation of this study is that it is a post hoc analysis of a phase 2 trial. The exclusion of 76 patients from the original study population is an additional limitation. However, the subgroup of analyzed patients was generally similar to the original study population

with respect to several key baseline characteristics (age, BMI, and lumbar spine BMD at baseline). The patient sample also excluded women under age 55, men of any age, and patients with secondary sources of osteoporosis, such as chronic glucocorticoid steroid use, so the results presented here cannot be extrapolated beyond the current study population.

These results help to differentiate further abaloparatide-SC from teriparatide in terms of potential effects on skeletal microarchitecture as determined indirectly by TBS, and provide additional support for the development of abaloparatide-SC as a new anabolic treatment for postmenopausal osteoporosis.

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#### Compliance with ethical standards

**Conflicts of interest** JPB is a consultant for Radius Health, Inc., Shire, Amgen, Eli Lilly, and Ultragenyx.

GH, LAF, AGH, are employees of Radius Health, Inc., and own company stock.

KB is an employee of Radius Health, Inc.

ES and JRZ have nothing to disclose.

BZL has been a consultant for Merck, and has been a consultant for and received research funding from Amgen and Eli Lilly.

DH is co-owner of the trabecular bone score (TBS) patent and is a part-time employee of Medimaps Group, and owns company stock.

**Statement of informed consent** All patients had provided informed written consent prior to their participation, in accordance with the Declaration of Helsinki for research on human subjects.

ABL-SC, abaloparatide-SC; SEM, standard error of the mean; TBS, trabecular bone score; TPTD, teriparatide.

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