Effect of Abaloparatide on Bone Mineral Density and Fracture Incidence in a Subset of Younger Postmenopausal Women with Osteoporosis at High Risk for Fracture

Kenneth G. Saag, MD[1]; Setareh A. Williams, PhD[2]; Yamei Wang, PhD[2]; Richard J. Weiss, MD[2]; and Jane A. Cauley, DrPH[3]

[1]Department of Medicine, University of Alabama, Birmingham, AL, USA; [2]Radius Health Inc, Waltham, MA, USA; and [3]School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

ABSTRACT

Purpose: Current treatment guidelines recommend treatment for postmenopausal women with a T score <−2.5 regardless of age. This subgroup analysis evaluated the efficacy and safety of abaloparatide in younger postmenopausal women considered to be at high risk for fracture.

Methods: Subgroup analysis of women in the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) trial who were <65 years old and met modified utilization management criteria (baseline T score ≤−2.5 [any site] and ≥1 prevalent vertebral and/or ≥1 prior clinical fracture within 5 years of randomization).

Findings: A total of 296 women (age range, 49−64 years) were included. Significant increases in bone mineral density from baseline were observed for abaloparatide versus placebo at all 3 sites at 6 months ($p < 0.01$ for total hip and femoral neck; $p < 0.0001$ for lumbar spine), 12 months ($p < 0.0001$ at all 3 sites), and 18 months ($p < 0.0001$ at all 3 sites). Fracture rates were numerically lower for abaloparatide versus placebo, consistent with the overall trial results, although the differences were not statistically significant. The number needed to treat to prevent 1 additional vertebral fracture after 18 months of treatment versus placebo was 18 for abaloparatide and 21 for teriparatide. The number needed to treat had nonsignificant trends toward lower values with abaloparatide versus teriparatide for nonvertebral fractures (23 vs 40) and clinical fractures (16 vs 73) and similar for major osteoporotic fractures (24 vs 27). The safety profile was consistent with the overall ACTIVE population.

Implications: Findings of this subgroup (post hoc) analysis are consistent with the overall ACTIVE population. Abaloparatide appears to be effective and well tolerated in this subgroup of younger postmenopausal women. ClinicalTrials.gov identifier: NCT01343004. (*Clin Ther*. 2020;42:1099−1107)

Key words: abaloparatide, nonvertebral fracture, number needed to treat, osteoporosis, vertebral fracture.

INTRODUCTION

Osteoporosis is a significant global health concern that is the cause of >2 million fractures annually in the United States.[1,2] Postmenopausal women >65 years of age are at the greatest risk for an osteoporotic fracture.[3] In addition, changes in bone mineral density (BMD) begin during late perimenopause or menopause,[4,5] and 1 of every 2 women >50 years of age is predicted to experience an osteoporosis-related fracture during her lifetime.[3] Pharmacotherapy is often not initiated for postmenopausal women <65

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years of age; however, sentinel fractures (most commonly at the wrist in US women) in this subpopulation are associated with functional decline, an increased risk for future fractures, and higher mortality risk.[6]

A recent study of Medicare enrollees found that the US age-adjusted hip fracture rates decreased from 2002 to 2012. More recently, though, the decrease has plateaued, and the fracture rate is potentially increasing, with higher than expected rates from 2013 to 2015.[7] A similar trend has been observed in a population of commercial and Medicare Advantage health plan enrollees.[8] The change in the hip fracture incidence trend is associated with decreasing rates of screening, diagnosis, and treatment of patients at risk for osteoporotic fractures.[7] Other factors beyond decreasing treatment rate, however, may also be contributing to the halt in previous decreases in hip fracture rates.[9] Because current US Preventive Services Task Force guidelines recommend screening for osteoporosis before the age of 65 years only in the presence of additional risk factors as determined by a formal risk assessment,[10] younger postmenopausal women may be at particular risk for underdiagnosis and undertreatment. Indeed, the International Society for Clinical Densitometry guidelines recommend dual-energy X-ray absorptiometry scanning for younger postmenopausal women with a risk factor for low bone mass (low weight, prior fracture, high-risk medication use, or a condition associated with bone loss)[11]; current treatment guidelines recommend treatment of women with a T score of <–2.5 regardless of age.[12] Further evaluation of the effectiveness of available therapies for the treatment of osteoporosis in this population is warranted.

Abaloparatide is a novel selective activator of the parathyroid hormone 1 receptor signaling pathway, which increases BMD and bone mass, improves bone microarchitecture and strength, and provides fracture risk reduction in preclinical and clinical studies.[13–18] It is included in the Endocrine Society's clinical practice guidelines as a recommended treatment option for patients classified as very high risk for fracture.[12]

In the 18-month, Phase III Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) study in women with postmenopausal osteoporosis, abaloparatide significantly increased BMD at the lumbar spine, total hip, and femoral neck and decreased the risk of vertebral, nonvertebral, clinical, and major osteoporotic fractures versus placebo.[19] Abaloparatide, when compared with teriparatide, given open label also produced a statistically significant reduction in major osteoporotic fractures and increased BMD, including significant improvements at the total hip and femoral neck at 6, 12, and 18 months and at the lumbar spine at 6 and 12 months, indicating an early effect with abaloparatide.[19]

The objective of this analysis was to evaluate the efficacy and safety of abaloparatide in a subset of women representative of commercial insurance enrollees considered to be at high risk for fracture (based on modified coverage criteria from a large US health insurance company).[20] The effectiveness of abaloparatide has been previously evaluated using data from the ACTIVE trial by calculating the number needed to treat (NNT), the mean number of patients who need to be treated to prevent 1 additional fracture.[21] The NNT to prevent 1 additional vertebral fracture with 18 months of treatment was 28 for abaloparatide versus 30 for teriparatide. The NNT was also lower for abaloparatide versus teriparatide for nonvertebral fractures (55 vs 92), clinical fractures (37 vs 59), and major osteoporotic fractures (34 vs 75). Only the difference in major osteoporotic fractures between abaloparatide and teriparatide was statistically significant ($p = 0.03$).

METHODS

Study Design

The randomized, multicenter ACTIVE study (NCT01343004), which included 2463 postmenopausal women aged 49–86 years with osteoporosis, has been previously described.[19] Briefly, women with a prior radiographic vertebral fracture or recent (within 5 years) nonvertebral fracture and a BMD T score of ≤–2.5 and >–5.0 (if aged ≤65 years) or ≤–2.0 or >–5.0 (if aged >65 years) were included in the study. Women >65 years of age with no prior fracture and a lumbar spine or femoral neck BMD T score of ≤–3.0 or >–5.0 were also eligible. Participants were randomly assigned 1:1:1 to double-blind, daily abaloparatide 80 μg subcutaneously, matching placebo subcutaneously, or open-label teriparatide 20 μg subcutaneously for 18 months.

Randomization was accomplished with randomly generated blocks of 6 to ensure balance between the treatment groups. Placebo was similarly formulated to abaloparatide but without active abaloparatide and was designed to deliver the same volume of fluid (supplied as a 1.5-mL type I glass cartridge).

This subgroup analysis included women in the ACTIVE study who were <65 years of age and who met modified utilization management criteria (baseline T score at any site of ≤−2.5 and a prevalent vertebral and/or at least 1 prior clinical fracture within 5 years of randomization). The modified utilization management criteria were based on coverage criteria for abaloparatide from a large US health insurance company.[20]

The ACTIVE study was approved by the ethics committee and institutional review board at every participating institution and was conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Study End Point

Study end points were assessed as previously described.[19] The primary end point was incidence of ≥1 new vertebral fractures from baseline to 18 months in women treated with abaloparatide versus placebo. New vertebral fractures included morphometric fractures assessed by blinded radiographic review, according to the method of Genant et al.[22]

Additional end points included percentage change from baseline in lumbar spine, total hip, and femoral neck BMD at 6, 12, and 18 months and time to first incidence of nonvertebral fracture, clinical fracture, and major osteoporotic fracture. Nonvertebral fractures included clinical fractures associated with low trauma, excluding those of the spine, sternum, patella, toes, fingers, skull, and face. Clinical fractures were defined as all fractures, regardless of the level of trauma, that would cause a patient to seek medical care, including clinical spine fractures. Major osteoporotic fractures encompassed high- or low-trauma fractures of the upper arm, wrist, hip, or clinical spine.

Statistical Analysis

Statistical analyses were performed as previously described.[19] Briefly, between-treatment differences in the incidence of new vertebral fracture were compared using the Fisher exact test in the modified intent-to-treat population (all intent-to-treat participants with both pretreatment and postbaseline spine radiographs). The percentage change from the ACTIVE study's baseline in BMD for total hip, femoral neck, and lumbar spine was analyzed using an analysis of covariance model, with missing data imputation by last observation carried forward.

The NNT to prevent 1 additional fracture was calculated as the reciprocal of the absolute risk reduction (difference in Kaplan−Meier event rate or difference in vertebral-fracture incidence) between the abaloparatide and placebo groups and the teriparatide and placebo groups. The incidence and severity of adverse events (AEs) were assessed from baseline through the 30-day follow-up period.

Treatment subgroup interactions were assessed by the Breslow−Day test for vertebral fractures, Cox proportional hazards regression model for nonvertebral fractures, and an analysis of covariance model for BMD.

RESULTS

Patient Characteristics

Of the 2463 patients from the ACTIVE study, a total of 296 women met the inclusion criteria for this subgroup analysis: 94 in the abaloparatide group, 103 in the placebo group, and 99 in the teriparatide group. The overall median age was 60 years (range, 49−64 years) (Table I).

At baseline, 92 (31%) had a prevalent vertebral fracture, and 234 (79%) reported ≥1 prior nonvertebral fractures (most commonly wrist, followed by forearm) in the past 5 years. The mean femoral neck T score was −2.1 in the abaloparatide group and −2.0 in the placebo and teriparatide groups. The mean total hip T scores were −1.9, −1.8, and −1.7, and the mean lumbar spine T scores were −3.0, −3.0, and −2.9 in the abaloparatide, placebo, and teriparatide groups, respectively.

BMD in Younger Patients at High Risk For Fracture From the ACTIVE Trial

Significant increases in BMD from baseline were observed for abaloparatide versus placebo at all 3 sites (total hip, femoral neck, and lumbar spine) at 6 months ($p < 0.01$ for total hip and femoral neck and $p < 0.0001$ for lumbar spine), 12 months ($p < 0.0001$ at all 3 sites), and 18 months

Table I. Baseline characteristics in a younger subset of patients at high risk for fracture from the ACTIVE trial.

Characteristic	ABL ($n = 94$)	PBO ($n = 103$)	TPTD ($n = 99$)
Age, y			
Mean (SD)	59.4 (3.6)	59.9 (3.3)	58.8 (3.8)
Median (range)	60.5 (49–64)	60.0 (50–64)	60.0 (50–64)
Time since menopause, mean (SD), y	11.1 (4.8)	12.1 (5.7)	11.1 (4.7)
BMI, mean (SD), kg/m^2	24.5 (3.2)	24.9 (3.1)	25.1 (3.5)
Race, No. (%)			
White	91 (96.8)	99 (96.1)	92 (92.9)
Asian	1 (1.1)	2 (1.9)	2 (2.0)
Black or African American	1 (1.1)	0 (0.0)	4 (4.0)
Other	1 (1.1)	2 (1.9)	1 (1.0)
BMD T score, mean (SD)			
Total hip	−1.89 (0.71)	−1.79 (0.72)	−1.67 (0.69)
Femoral neck	−2.09 (0.57)	−2.03 (0.65)	−1.95 (0.64)
Lumbar spine	−3.00 (0.63)	−2.99 (0.64)	−2.90 (0.58)
≥1 Prevalent vertebral fracture, No. (%)	34 (36.2)	25 (24.3)	33 (33.3)
≥1 Prior nonvertebral fracture in the past 5 years, No. (%)	72 (76.6)	88 (85.4)	74 (74.7)

ABL = abaloparatide; ACTIVE = Abaloparatide Comparator Trial in Vertebral Endpoints; BMD = bone mineral density; BMI = body mass index; PBO = placebo; TPTD = teriparatide.

($p < 0.0001$ at all 3 sites), which was consistent with the overall ACTIVE population results (Fig. 1). At 18 months, the mean changes in BMD from baseline were 3.20% for abaloparatide versus −0.12% for placebo at the total hip (difference in least-squares mean, 3.29; 95% CI, 2.47–4.11); 2.71% for abaloparatide versus −0.67% for placebo at the femoral neck (difference in least-squares mean, 3.39; 95% CI, 2.40–4.39); and 7.81% for abaloparatide versus −0.17% for placebo at the lumbar spine (difference in least-squares mean, 7.99; 95% CI, 6.71–9.27). BMD improvements with abaloparatide versus placebo were consistent across age subgroups (≤60 vs >60 years) (Supplemental Figure 1).

BMD results were similar for teriparatide versus placebo. Significant increases ($p < 0.001$) in BMD from baseline were observed for all 3 sites (total hip, femoral neck, and lumbar spine) at all 3 time points, except that no significant changes were found at the total hip and femoral neck at 6 months. Change in BMD from baseline was not significantly different for abaloparatide versus teriparatide.

Fracture Incidence and NNT in Younger Patients at High Risk for Fracture From the ACTIVE Trial

Fracture incidence rates were very low in this subpopulation, with no statistically significant differences across treatment groups for any fracture site. The new vertebral-fracture incidence rates were 1.3% (n = 1 of 80) in the abaloparatide group, 7.1% (n = 6 of 85) in the placebo group, and 2.3% (n = 2 of 88) in the teriparatide group. There were 1 (abaloparatide), 5 (placebo), and 3 (teriparatide) patients with a nonvertebral fracture; 2 (abaloparatide), 8 (placebo), and 7 (teriparatide) patients with a clinical fracture; and 2 (abaloparatide), 6 (placebo), and 3 (teriparatide) patients with a major osteoporotic fracture.

The NNT in patients <65 years of age from the ACTIVE group (based on vertebral-fracture incidence) to prevent 1 additional vertebral fracture after 18 months of treatment versus placebo was 18 for abaloparatide and 21 for teriparatide (Fig. 2A). The NNT (based on the Kaplan–Meier event rate) to prevent 1 additional fracture after 18 months of

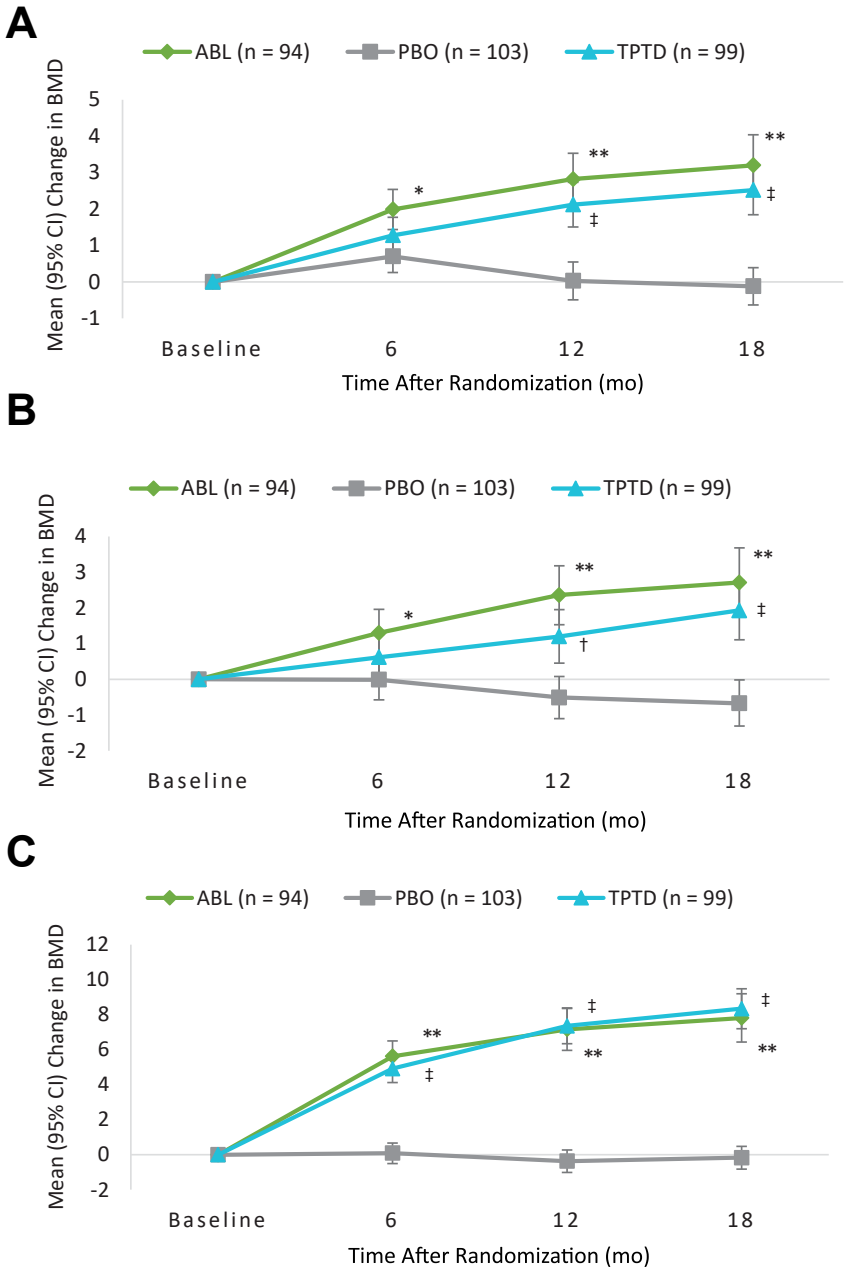

Figure 1. Change from baseline in bone mineral density (BMD) (A) total hip, (B) femoral neck, and (C) lumbar spine. Missing BMDs were imputed using the method of last observation carried forward. *$p < 0.01$ for abaloparatide (ABL) versus placebo (PBO); **$p < 0.0001$ for ABL versus PBO; †$p < 0.001$ for teriparatide (TPTD) versus PBO; ‡$p < 0.0001$ for TPTD vs PBO.

treatment versus placebo was 23 for abaloparatide and 40 for teriparatide for nonvertebral fractures, 16 for abaloparatide and 73 for teriparatide for clinical fractures, and 24 for abaloparatide and 27 for teriparatide for major osteoporotic fractures (Fig. 2B).

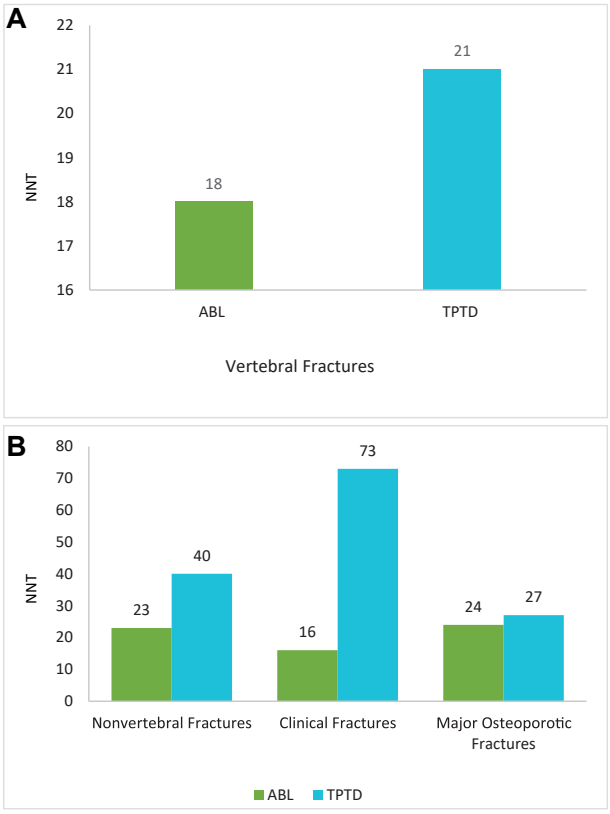

Figure 2. Number needed to treat (NNT) to prevent 1 additional fracture calculated as reciprocal of the absolute risk reduction based on difference in fracture incidence. (A) NNT for vertebral fractures; (B) NNT for nonvertebral, clinical, and major osteoporotic fractures. ABL = abaloparatide; TPTD = teriparatide.

Interactions

No statistically significant interactions occurred between treatment and a younger (age <65 years) subset of patients at high risk of fracture versus women with all other baseline characteristics on the efficacy parameters tested (p-values $\geq$ 0.3).

Safety Outcomes and AEs in Younger Patients at High Risk for Fracture from the ACTIVE Group

Safety outcomes were consistent with those previously reported for the entire ACTIVE population.[19] The proportion of patients with $\geq$1 treatment-emergent AEs was similar between groups: abaloparatide, 84.0%; placebo, 82.5%; and teriparatide, 87.9%. The most frequently observed AEs that occurred in $\geq$5% of patients in any group are listed in Table II.

Serious treatment-emergent AEs occurred in 6 patients (6.4%) in the abaloparatide group, 11 patients (10.7%) in the placebo group, and 10 patients (10.1%) in the teriparatide group. Nine patients (9.6%) in the abaloparatide group, 8 (7.8%) in the placebo group, and 4 (4.0%) in the teriparatide group experienced an AE that led to study discontinuation (Table II).

DISCUSSION

Osteoporosis screening is recommended for all women $\geq$65 years of age[11,23]; however, by 60 years of age, half of all white women have osteopenia or osteoporosis.[24] Current guidelines recommend screening for postmenopausal women <65 years of age in the presence of risk factors, such as low body weight, long-term systemic glucocorticoid therapy, family history of osteoporotic fracture, early menopause, current smoking, or excessive alcohol consumption[23] or if they are at increased risk for fracture using a formal clinical-risk assessment tool.[10] In general, risk assessment includes a BMD T score of $\leq$–2.5 as the diagnostic threshold for osteoporosis and increased fracture risk; however, half of all fragility fractures occur in patients with a BMD in the osteopenia range (T score of –1 to –2.5), suggesting that BMD alone does not present a full picture of a woman's risk for fracture.[3] A history of prior vertebral, hip, or multiple nonvertebral and nonhip fractures is an independent predictor of future fractures[25,26] but may be overlooked in patients with BMD >–2.5. Furthermore, although it has been suggested that trabecular bone score in combination with the fracture risk assessment tool (FRAX) is more sensitive than either method alone,[27] current risk assessment tools do not include measures of bone quality and microarchitecture, such as trabecular bone score, which could be contributing to fracture risk. Indeed, diagnosis and treatment of osteoporosis are low in women and men who sustained a fracture in both commercial and Medicare Advantage populations. Although these rates increased significantly after a fracture, they still remained below guideline-recommended levels.[28] Many women have a sentinel event before being diagnosed with osteoporosis and,

Table II. Number (percentage) of safety outcomes and AEs.

Outcome or AE	ABL ($n = 94$)	PBO ($n = 103$)	TPTD ($n = 99$)
All TEAEs	79 (84.0)	85 (82.5)	87 (87.9)
Serious TEAEs	6 (6.4)	11 (10.7)	10 (10.1)
Deaths	0 (0.0)	1 (1.0)	0 (0.0)
AEs leading to discontinuation	9 (9.6)	8 (7.8)	4 (4.0)
Most frequently observed AEs[a]			
Headache	12 (12.8)	12 (11.7)	6 (6.1)
Nausea	10 (10.6)	4 (3.9)	7 (7.1)
Hypercalciuria	9 (9.6)	1 (1.0)	6 (6.1)
Back pain	8 (8.5)	12 (11.7)	9 (9.1)
Nasopharyngitis	7 (7.4)	9 (8.7)	9 (8.1)
Constipation	7 (7.4)	5 (4.9)	6 (6.1)
Dizziness	7 (7.4)	3 (2.9)	3 (3.0)
Palpitations	7 (7.4)	0 (0.0)	1 (1.0)
Arthralgia	5 (5.3)	10 (9.7)	11 (11.1)
Hypertension	5 (5.3)	9 (8.7)	5 (5.1)
Hypercholesterolemia	5 (5.3)	1 (1.0)	3 (3.0)
Pain in extremity	4 (4.3)	7 (6.8)	5 (5.1)
Influenza	4 (4.3)	8 (7.8)	3 (3.0)
Spinal pain	3 (3.2)	3 (2.9)	5 (5.1)
Upper respiratory tract infection	2 (2.1)	7 (6.8)	7 (7.1)
Blood triglycerides increased	2 (2.1)	1 (1.1)	5 (5.1)
Contusion	1 (1.1)	5 (4.9)	5 (5.1)
Vertigo	1 (1.1)	3 (2.9)	5 (5.1)
Creatinine renal clearance increased	1 (1.1)	0 (0.0)	5 (5.1)
Myalgia	1 (1.1)	0 (0.0)	5 (5.1)

ABL = abaloparatide; AE = adverse event; PBO = placebo; TEAE, treatment-emergent adverse event; TPTD = teriparatide.
[a] Occurring in ≥5% of patients in any group.

consequently, are at increased risk for subsequent fracture.[25] In such patients, early access to anabolic therapy has the potential to decrease the risk of future fracture events, including downstream morbidity and mortality risks, as well as associated health care costs.

This study examined the safety and efficacy of the anabolic agent abaloparatide in a subgroup of women <65 years of age with a prior fracture and baseline T score of ≤−2.5 (any site) from the ACTIVE trial. Abaloparatide resulted in significant improvements in BMD compared with placebo in this subgroup. A nonsignificant, numerical risk reduction for vertebral and nonvertebral fractures was also seen, although these analyses were limited by the small number of fractures in this analysis. Efficacy and safety outcome results for this subgroup were generally consistent with the overall ACTIVE population.

In this analysis, the NNT was numerically less but not statistically significant with abaloparatide compared with teriparatide for nonvertebral fractures and clinical fractures but similar for vertebral fractures, wrist fractures, and major osteoporotic fractures. These results are consistent with data reported by Reginster et al[21] for the full active population, for which the NNT was also less with abaloparatide versus teriparatide for nonvertebral

and clinical fractures. In contrast with this analysis, Reginster et al[21] also found that the NNT was less with abaloparatide versus teriparatide for major osteoporotic fractures, whereas our study found a similar NNT between treatment groups.

There are limitations to our study. The ACTIVE trial was not powered for subgroup analysis, and the number of patients included in this subgroup analysis was relatively small. Furthermore, there were no prespecified measures for family-wise type I error control for multiple testing related to subgroup analyses. Therefore, this post hoc subgroup analysis, like any other subgroup analysis, either preplanned or post hoc, could be a chance finding.[29] As such, *p* values in this article should be interpreted with caution. In addition, because teriparatide was administered open label, reporting bias for subjective measures may have occurred.

Results from this subgroup analysis support the use of abaloparatide in a younger population of women who are at risk for fracture and whose coverage is through commercial insurance.

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DISCLOSURES

Dr Saag is a consultant to Amgen, Eli Lilly, and Radius Health, Inc., and has received research support from Amgen and Eli Lilly and Company. Drs Williams, Wang, and Weiss are employees of and own company stock in Radius Health Inc. Dr Cauley and the other authors have indicated that they have no other conflicts of interest regarding the content of this article.

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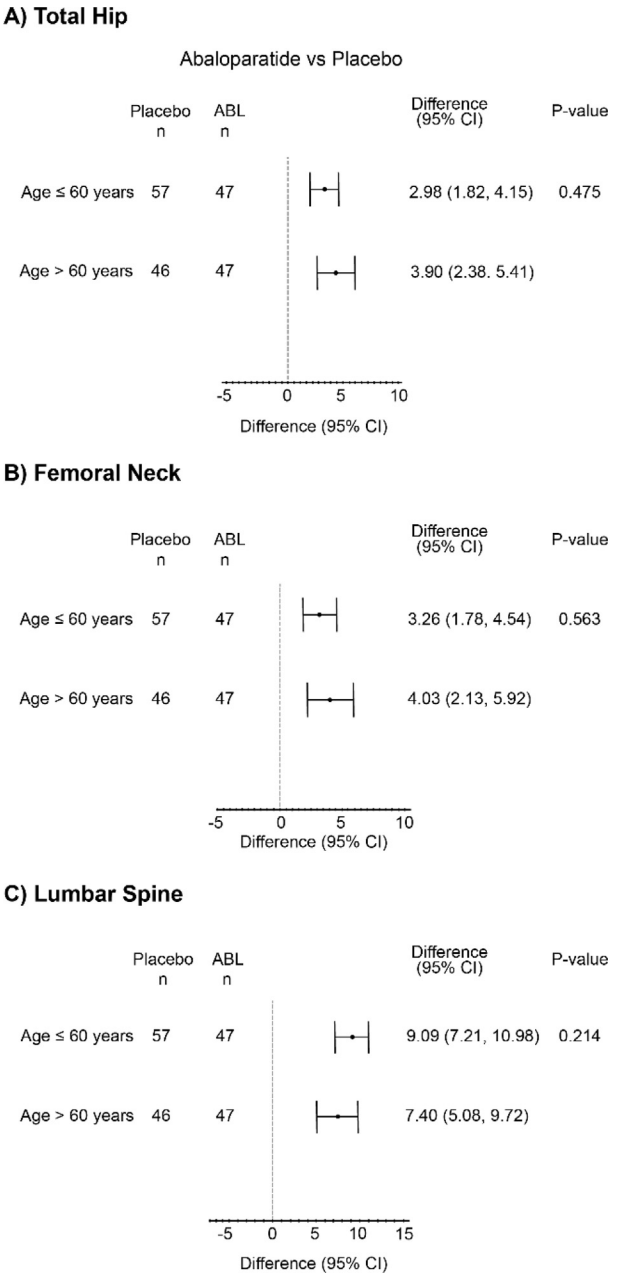
Address correspondence to: Richard J. Weiss, MD, 550 E. Swedesford Rd, Ste 370, Wayne, PA, 19087, USA. E-mail: rweiss@radiuspharm.com

APPENDIX



Supplementary Figure 1. Least-Squares Mean Difference in BMD in Patients Aged ≤60 Years vs >60 years. ABL, abaloparatide; BMD, bone mineral density; ITT, intent to treat; PBO, placebo; TPTD, teriparatide.