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Effect of abaloparatide on fracture incidence and bone mineral density in postmenopausal women with osteoporosis at highest risk for fracture

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Abstract

Objective: This post hoc analysis evaluated the efficacy of abaloparatide treatment in a subgroup of postmenopausal women from the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE; NCT01343004) study who met high fracture risk criteria (defined in several professional society guidelines).

Methods: Women from ACTIVE meeting ≥1 of the following fracture risk criteria were included: fracture within the past 12 months or prevalent vertebral fracture, baseline T score of < −3.0 at any site, very high fracture risk probability by FRAX (ie, 10-yr major osteoporotic fracture > 30% or hip fracture > 4.5%), or multiple prior fractures at baseline since age ≥ 45 years.

Results: A total of 2,026 participants met ≥1 fracture risk criteria defined in clinical guidelines (abaloparatide, n = 664; placebo, n = 677; teriparatide, n = 685). New vertebral fracture risk was reduced in participants receiving abaloparatide (4 [0.72%]) and teriparatide (6 [0.99%]) versus placebo (28 [4.77%]; both $P < 0.0001$). Estimated Kaplan-Meier cumulative incidence of nonvertebral fracture was 3.0%, 5.3%, and 3.0% in the abaloparatide, placebo, and teriparatide groups, respectively; 4.0%, 9.0%, 4.3% for clinical fracture; 1.6%, 6.8%, 3.0% for major osteoporotic fractures; and 1.1%, 2.1%, 2.1% for wrist fracture. Abaloparatide was associated with bone mineral density gains from baseline at the lumbar spine, total hip, and femoral neck at all time points (6, 12, and 18 mo; $P < 0.0001$ for all). Common adverse events reported in participants treated with abaloparatide were hypercalciuria (11.5%), dizziness (11.0%), and arthralgia (8.9%).

Conclusions: Abaloparatide reduced fracture incidence and increased bone mineral density in participants at highest fracture risk, consistent with the overall ACTIVE study.

Key Words: Abaloparatide, Bone mineral density, Clinical fracture, High fracture risk, Osteoporotic fracture, Vertebral fracture.

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Medicare claims data show that 10% of women aged ≥ 65 years with a clinical fracture will sustain another fracture within the next year, and 31% will sustain another fracture within 5 years.[1] Following an initial fracture, mortality rates were found to be 19% and 64% within 1 and 5 years, respectively.[1] These statistics highlight the importance of identifying postmenopausal

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Data Sharing 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.

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women at risk for fracture, and the critical need to prescribe appropriate therapies that can rapidly improve bone mineral density (BMD) and reduce fracture risk in these individuals.[2,3]

Among different organizations, criteria for the identification and classification of women with osteoporosis at high fracture risk are varied. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) consider individuals to be at a very high fracture risk if they meet any of the following criteria: a recent fracture within the past 12 months, multiple fractures, a history of injurious falls or a high risk for falls, fracturing while on an approved osteoporosis treatment or medications known for causing skeletal harm (eg, long-term glucocorticoids), a very low T score (eg, less than −3.0), or very high fracture risk probability (ie, major osteoporotic fracture [MOF] > 30% or hip fracture > 4.5%) by FRAX or another validated fracture risk algorithm.[4] Other organizations (eg, American College of Obstetricians and Gynecologists [ACOG], Endocrine Society [ES], and The Menopause Society) utilize similar criterion.[5-9] For example, both The Menopause Society and ACOG criteria for very high fracture risk classification include BMD loss (vs experiencing a fracture for AACE/ACE) while on antiresorptive treatment,[8,9] while ES guidelines include severe or multiple vertebral fractures or a low BMD T score at the hip or spine of < −2.5 (vs < −3.0 for AACE/ACE) as part of their high fracture risk criteria.[5,7]

Anabolic medications (eg, abaloparatide, teriparatide, and romosozumab), which increase bone formation, followed by antiresorptive treatments (eg, alendronate or denosumab), which reduce bone resorption, have been shown to be effective at decreasing fracture risk and increasing BMD.[10] For individuals at very high fracture risk, the AACE/ACE guidelines recommend treatment with anabolic therapies or antiresorptive agents.[4,11] Other guidelines (ie, ACOG, ES, and The Menopause Society) also recommend initial treatment with an anabolic agent for individuals at high or very high risk of fracture, such as those with severe or multiple vertebral fractures.[5,7-9]

Abaloparatide is a synthetic, 34-amino acid peptide that selectively binds to the G protein-coupled RG conformation of the parathyroid hormone type 1 receptor, which favors increased bone formation while limiting effects on bone resorption markers.[12,13] Abaloparatide is indicated for the treatment of postmenopausal women with osteoporosis at high risk of fracture and to increase BMD in men with osteoporosis at high risk of fracture.[14]

In the randomized, double-blind, multicenter phase 3 Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE; ClinicalTrials.gov identifier: NCT01343004) study, postmenopausal women with osteoporosis treated with abaloparatide for 18 months had a significantly reduced risk of new vertebral fracture (0.6% vs 4.2%), nonvertebral fracture (2.7% vs 4.7%), clinical fracture (4.0% vs 8.3%), and MOF (1.5% vs 6.2%) compared to participants who received placebo.[12] At 18 months, abaloparatide also significantly decreased the risk of MOF compared to teriparatide; however the ACTIVE study was not powered to show superiority of abaloparatide versus teriparatide.[12] Bone mineral density at 6, 12, and 18 months increased significantly at the lumbar spine, total hip, and femoral neck in participants treated with abaloparatide versus placebo.[12] When compared with teriparatide, abaloparatide treatment significantly increased BMD at the total hip and femoral neck at all study time points, and at the lumbar spine at 6 and 12 months.[12]

This post hoc analysis evaluated the efficacy of abaloparatide compared to placebo and teriparatide in reducing fractures in a subgroup of participants from the ACTIVE study who were determined to be at the highest risk of fracture based on a composite of criteria derived from several clinical practice guidelines and data available from the ACTIVE trial.

METHODS

Study design

In ACTIVE, postmenopausal women (N = 2,463) were randomized 1:1:1 to either blinded daily subcutaneous injections of abaloparatide 80 μg (n = 824) treatment or placebo (n = 821), or open-label teriparatide 20 μg (n = 818) for 18 months.[12] Eligibility criteria were previously described in Miller et al.[12] Briefly, participants were eligible if they had a BMD T score ≤ −2.5 and > −5.0 at the lumbar spine or femoral neck with at least 2 mild or 1 moderate vertebral fracture, or a history of a low trauma fracture within the past 5 years.[12] Women aged > 65 years were eligible for study participation if they had a T score ≤ −2.0 and > −5.0 and met fracture criteria, or had a T score ≤ −3.0 and > −5.0 if they did not meet fracture criteria.[12]

The ACTIVE study was approved by the ethics committee at every participating institution and was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki.[12] All participants completed an extensive informed consent evaluation to participate in the study.[12] Participants provided written consent and the protocol was approved by the respective institutional review boards.

ACTIVE highest risk subpopulation

Postmenopausal women included in this subgroup post hoc analysis had to meet at least one of the four following criteria at baseline to be considered at highest fracture risk; 1) a fracture within the past 12 months or ≥ 1 prevalent vertebral fracture, 2) very low baseline T score of < −3.0 at any site, 3) a very high fracture risk probability (eg, MOF > 30% or hip fracture > 4.5%) as assessed by FRAX (a fracture risk assessment tool), or 4) multiple prior fractures at baseline since the age of ≥ 45 years. These criteria were selected based on data available from the ACTIVE trial and criteria for very high fracture risk from several clinical practice guidelines.

Study assessments

Overall, new incidence of vertebral, nonvertebral, wrist, and MOFs in participants who met the highest fracture risk criteria from the ACTIVE study was evaluated at 19 months (18 mo of treatment plus 1 mo of

follow-up) to compare the efficacy of abaloparatide versus placebo and teriparatide. Vertebral fractures were assessed by 2 blinded radiologists based on pretreatment and postbaseline lumbar spine x-rays and graded according to the Genant Severity Scale. Nonvertebral fractures (including wrist, clinical, and MOF) were self-reported and verified from source documents. In addition to examining the overall fracture incidence of participants meeting at least one of the highest risk study criteria, the incidence of vertebral, nonvertebral, and clinical fracture was determined by each study criteria individually. Clinical fractures included all fractures that resulted in a participant seeking medical care. A MOF included high or low trauma fractures of the clinical spine, hip, upper arm, or wrist. Change in BMD from baseline at the lumbar spine, total hip, and femoral neck was analyzed at 6, 12, and 18 months during the treatment period in participants treated with abaloparatide compared with placebo and teriparatide.[12] All efficacy endpoints except new vertebral fractures were evaluated in the intention to treat (ITT) population (all participants randomized into the study and received a study medication kit on day 1).[12] New vertebral fractures were evaluated in the modified ITT (mITT) population (all ITT participants who had both pretreatment and postbaseline lumbar spine x-rays).[12] The safety population included all participants who had received at least one dose of study medication.

Statistical analysis

The *P* value was derived from Fisher's exact test, which was used to evaluate the incidence of new vertebral fractures in the mITT population when comparing abaloparatide to placebo and teriparatide to placebo.[12] The Kaplan-Meier (KM) method was utilized to evaluate the event rate of nonvertebral, clinical, major osteoporotic, and wrist fractures in the ITT population. Cumulative KM estimates determined event rates at 19 months (the entire observational period including 18 mo of treatment and 1 mo of follow-up). A Cox proportional hazard model was used to calculate hazard ratios, and *P* values were generated from the log-rank test. An analysis of covariance model was used to assess change in baseline BMD at the lumbar spine, total hip, and femoral neck in the ITT population, and any missing data that was imputed by the last observation was carried forward. The dependent variable was BMD percent change from baseline. The analysis covariance model included factors of treatment, visit, treatment and visit interaction, DXA scanner model, and baseline BMD as the covariate. All *P* values are presented without adjustment for multiple comparisons. Statistical analyses were performed using SAS version 9.4.[12]

RESULTS

Study population

Of the 2,463 participants included in the ACTIVE study, 2,026 (abaloparatide, n = 664; placebo, n = 677; teriparatide, n = 685) met the highest fracture risk criteria and were included in the current analysis. Baseline mean age was 69.3 years, with 28.9% of participants having ≥ 1 prevalent vertebral fracture(s) and 31.0% experiencing ≥ 1 nonvertebral fracture(s) within the past 5 years (Table 1). Of the 2,026 participants, 1,747 (abaloparatide, n = 555; placebo, n = 587; teriparatide, n = 605) and 2,023 (abaloparatide, n = 662; placebo, n = 676; teriparatide, n = 685) met criteria for inclusion in the mITT and safety populations, respectively. Baseline demographics, clinical characteristics, and fracture history were balanced between the three study groups (abaloparatide, placebo, and teriparatide) (Table 1).

In the ITT population, evaluation by individual high-risk criteria at baseline showed that 736 (36.3%) participants (abaloparatide, n = 227; placebo, n = 238; teriparatide, n = 271) had experienced a fracture within the prior 12 months or had ≥ 1 prevalent vertebral fracture. Within the ITT population, 1,470 (59.7%) participants (abaloparatide, n = 498; placebo, n = 493; teriparatide, n = 479) had a baseline BMD T score of < −3.0 at any site; 611 (24.8%) participants (abaloparatide, n = 188; placebo, n = 212; teriparatide, n = 211) experienced multiple fractures since 45 years of age, and 950 (38.6%) participants (abaloparatide, n = 310; placebo, n = 321; teriparatide, n = 319) were considered at very high fracture risk by FRAX (MOF > 30% or hip fracture > 4.5%).

Baseline characteristics for the 437 (17.7%) participants from the ACTIVE study that did not meet the criteria for highest risk for fracture are available in Supplemental Table 1 (http://links.lww.com/MENO/B350).

Efficacy

New vertebral fractures

In participants who met any of the four highest fracture risk study criteria, the incidence of new vertebral fracture was lower in the abaloparatide and teriparatide groups when compared to placebo (abaloparatide, 4/555 [0.72%]; placebo, 28/587 [4.77%]; teriparatide, 6/605 [0.99%]). The absolute risk reduction (95% confidence interval [CI]) was 4.05% (2.22-6.13) for abaloparatide and 3.78% (1.93-5.89) for teriparatide (Fig. 1). The relative risk reduction was 85% for abaloparatide and 79% for teriparatide versus placebo. These reductions were clinically meaningful compared to placebo ($P < 0.0001$ for both abaloparatide and teriparatide).

New vertebral fractures by fracture risk criteria

In participants with a prior fracture in the last 12 months or vertebral fracture at baseline, those treated with abaloparatide and teriparatide experienced vertebral fracture at a lower rate compared to placebo (abaloparatide, 1/189 [0.53%]; placebo, 16/207 [7.73%]; teriparatide, 6/242 [2.48%]) with absolute risk reductions of 7.20% (3.42-11.68) and 5.25% (1.19-9.90) (abaloparatide $P = 0.0003$; teriparatide $P = 0.0144$) (see Supplemental Fig. 1A, http://links.lww.com/MENO/B350). In participants with a low T score at any site, 3/411 (0.73%) participants treated with abaloparatide, 17/431 (3.94%) receiving placebo, and 3/425 (0.71%) treated with teriparatide experienced a vertebral fracture during the study. The absolute risk reduction in

TABLE 1. Demographics and baseline characteristics, ITT population[a]

Characteristic	Abaloparatide (n = 664)	Placebo (n = 677)	Teriparatide (n = 685)	Overall (N = 2026)
Age, years				
Mean (SD)	69.3 (6.6)	69.2 (6.3)	69.2 (6.6)	69.3 (6.5)
Median (range)	69 (49, 85)	69 (50, 86)	69 (50, 84)	69 (49, 86)
Body mass index, mean (SD)	24.7 (3.4)	24.8 (3.5)	24.9 (3.5)	24.8 (3.5)
Race category, n (%)				
White	518 (78.0)	520 (76.8)	524 (76.5)	1,562 (77.1)
Asian	117 (17.6)	127 (18.8)	133 (19.4)	377 (18.6)
Black or African American	24 (3.6)	20 (3.0)	20 (2.9)	64 (3.2)
Other[b]	5 (0.8)	10 (1.5)	8 (1.2)	23 (1.1)
Region, n (%)				
Europe	354 (53.3)	366 (54.1)	364 (53.1)	1,084 (53.5)
South America	182 (27.4)	175 (25.8)	185 (27.0)	542 (26.8)
Asia	116 (17.5)	126 (18.6)	128 (18.7)	370 (18.3)
North America	12 (1.8)	10 (1.5)	8 (1.2)	30 (1.5)
Lumbar spine BMD T score				
n	663	677	685	2,025
Mean (SD)	−3.0 (0.9)	−3.0 (0.8)	−2.9 (0.9)	−3.0 (0.9)
Total hip BMD T score				
n	662	676	685	2,023
Mean (SD)	−2.0 (0.7)	−2.0 (0.8)	−1.9 (0.7)	−2.0 (0.7)
Femoral neck BMD T score				
n	662	676	685	2,023
Mean (SD)	−2.3 (0.6)	−2.3 (0.7)	−2.2 (0.7)	−2.2 (0.6)
≥ 1 Prevalent vertebral fracture(s), n/N (%)	177/664 (26.7)	188/676 (27.8)	220/685 (32.1)	585/2,025 (28.9)
≥ 1 Nonvertebral fracture within 5 yr prior to randomization, n (%)[c]	207 (31.2)	219 (32.3)	203 (29.6)	629 (31.0)
No prior fracture, n (%)	221 (33.3)	229 (33.8)	240 (35.0)	690 (34.1)

BMD, bone mineral density; ITT, intent to treat; SD, standard deviation.

[a]ITT population included participants who were randomized into the study and had received a study medication kit on day 1, if they had met at least one of the predefined, high fracture risk criteria. Includes participants that have had a nonvertebral fracture within 5 years prior to randomization by very high combined risks or prevalent vertebral fracture at baseline.

[b]Information regarding what was included in the "other" category is not available.

[c]Excludes fractures of the spine, sternum, patella, toes, fingers, skull, and facial bones.

vertebral fracture was 3.21% (1.19-5.55) for participants treated with abaloparatide and 3.24% (1.25-5.57) for participants receiving teriparatide (abaloparatide, $P = 0.0024$; teriparatide, $P = 0.0023$). Of the participants with multiple fractures since 45 years of age, 0/157 participants treated with abaloparatide had a vertebral fracture during the study, and 16/175 (9.14%) participants receiving placebo and 4/187 (2.14%) participants treated with teriparatide had a vertebral fracture, with an absolute risk reduction of 9.14% (4.96-14.33) in the abaloparatide group and 7.00% (2.29-0.36) in the teriparatide group when compared to placebo ($P < 0.0001$ and $P = 0.0047$, respectively). Of the participants with a high fracture risk as assessed by FRAX, 1/269 (0.37%), 18/285 (6.32%), and 2/290 (0.69%) participants in the abaloparatide, placebo, and teriparatide groups, respectively, experienced a new vertebral fracture

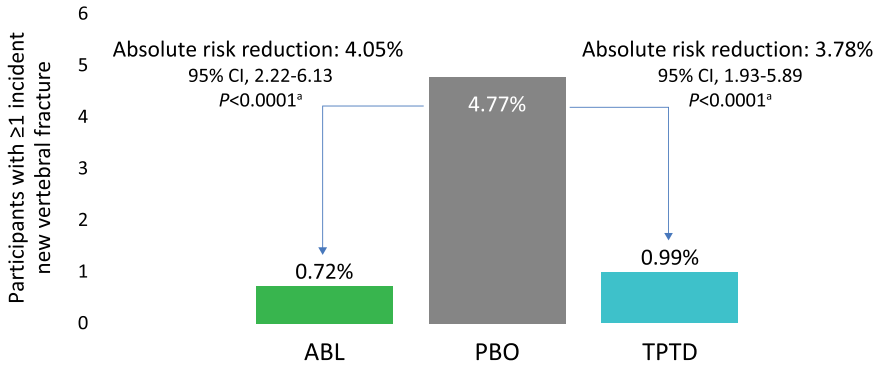

FIG. 1. Absolute risk reduction in new vertebral fracture in participants at highest risk for fracture at 18 months, mITT Population. ABL, abaloparatide; CI, confidence interval; ITT, intent to treat; mITT, modified ITT; PBO, placebo; TPTD, teriparatide. The mITT population includes all participants from the ITT population with both baseline and post baseline spine x-rays. [a]*P* value from Fisher's exact test.

during the study. Participants with a high fracture probability by FRAX assessment had absolute risk reductions of 5.94% (3.09-9.40) in the abaloparatide group and 5.63% (2.72-9.11) in the teriparatide group ($P < 0.0001$ and $P = 0.0002$, respectively, vs placebo).

Only 136 participants met all 4 study criteria at baseline, resulting in an inadequate sample size for treatment comparison.

Nonvertebral, wrist, clinical, and MOF

Kaplan-Meier cumulative incidence of nonvertebral fracture was 3.0%, 5.3%, and 3.0% in the abaloparatide, placebo, and teriparatide groups, respectively. Kaplan-Meier cumulative incidence of wrist fracture was 1.1%, 2.1%, and 2.1%, clinical fracture was 4.0%, 9.0%, and 4.3%, and MOF was 1.6%, 6.8%, and 3.0% in the abaloparatide, placebo, and teriparatide groups, respectively (Fig. 2). Reductions in the number of participants with nonvertebral (16/664 vs 30/677) or wrist fractures (6/664 vs 12/677) observed in participants treated with abaloparatide compared to placebo over 18 months were not significant. Likewise, the incidence of nonvertebral fractures (19/685) and wrist fractures (13/685) in participants treated with teriparatide were numerically decreased, but not significant when compared to placebo. The absolute risk reduction for nonvertebral fracture was −2.28% (−4.62 to 0.05) and −2.21% (−4.49 to 0.06) for participants treated with abaloparatide and teriparatide, respectively, when compared to placebo. Treatment with abaloparatide resulted in reductions ($P < 0.05$) in clinical fractures (22/664 vs 43/677) and MOFs (9/664 vs 30/677) when compared to placebo. Among participants treated with teriparatide, clinical fractures were reduced (27/685, $P < 0.05$), and MOF incidence was numerically reduced (19/685) when compared to placebo.

New nonvertebral fractures by fracture risk criteria

For participants with a fracture within the past 12 months or ≥1 prevalent vertebral fracture at baseline, estimated KM incidence for nonvertebral fracture was 4.3%, 6.5%, and 3.6% in the abaloparatide, placebo, and teriparatide groups, respectively (see Supplemental Fig. 1B, http://links.lww.com/MENO/B350). The estimated KM incidence of nonvertebral fracture for participants with baseline low T score was 2.8%, 5.5%, and 3.0% in the abaloparatide, placebo, and teriparatide groups, respectively. In the low T score group, only participants treated with abaloparatide had a reduction in nonvertebral fracture when compared to placebo ($P = 0.048$). Kaplan-Meier incidence of nonvertebral fracture was 3.9%, 6.4%, and 4.7% in participants who experienced multiple fractures since 45 years of age, and 3.2%, 5.5%, and 4.1% in participants with high fracture risk as assessed by FRAX for the abaloparatide, placebo, and teriparatide groups, respectively. The decreases in nonvertebral fractures for participants with multiple fractures or high fracture risk as assessed by FRAX were not significant for participants treated with abaloparatide or teriparatide when compared to placebo.

Clinical fractures by fracture risk criteria

Clinical fracture events categorized by treatment and baseline study criteria for highest fracture risk are available in Supplemental Figure 1C (http://links.lww.com/MENO/B350). Kaplan-Meier cumulative incidence of clinical fracture was numerically lower for both abaloparatide and teriparatide versus placebo in the following baseline subgroups: fracture within the past 12 months or ≥1 prevalent vertebral fracture at baseline (6.4%, 9.8%, 5.6%), multiple fractures since 45 years of age (6.5%, 10.2%, 6.8%), and MOF >30% or hip fracture >4.5% as assessed by FRAX (4.4%, 8.3%, 5.4%) in the abaloparatide, placebo, and teriparatide groups, respectively. The absolute risk reduction in clinical fracture incidence in the low T score subgroup was 6.76 (1.12-12.40) for abaloparatide ($P = 0.006$) and 6.61 (0.98-12.23) for teriparatide ($P = 0.012$) when compared to placebo.

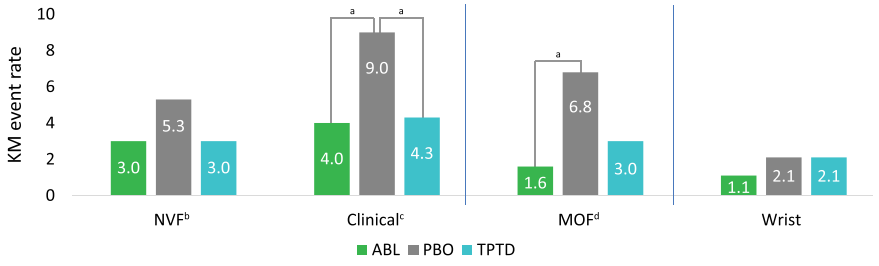

FIG. 2. Kaplan-Meier cumulative incidence rate of nonvertebral, clinical, major osteoporotic, and wrist fracture in participants at highest risk for fracture at 19 months, ITT population. The ITT population was used for the cumulative KM estimates to determine the percentage of nonvertebral fractures, clinical fractures, MOF, and wrist fractures at 19 months (the entire observational period including 18 mo of treatment and 1 mo of follow-up). Differences were not significant for ABL vs TPTD. ABL, abaloparatide; ITT, intent to treat; KM, Kaplan-Meier; MOF, major osteoporotic fracture; NVF, nonvertebral fracture; PBO, placebo; TPTD, teriparatide. [a]$P < 0.05$. [b]NVF were fractures that excluded those of the spine, sternum, patella, toes, fingers, skull, and face and those associated with high trauma. [c]Clinical fractures included all fractures causing a participant to seek medical care. *P* values were $P < 0.05$ for ABL vs PBO, and $P < 0.05$ for TPTD vs PBO. [d]MOF included high or low trauma fractures of the upper arm, wrist, hip, or clinical spine. *P* value was $P < 0.01$ for ABL vs PBO.

Fracture risk reduction in participants at lower fracture risk

Of the participants from ACTIVE who were excluded from the highest fracture risk analysis for not meeting the criteria for highest fracture risk, no participants treated with abaloparatide or teriparatide experienced a new vertebral fracture, compared to 2/124 (1.61%) participants in the placebo group. The absolute risk reduction was not significant for the abaloparatide (1.61 [−1.39 to 5.69]) or teriparatide (1.61% [−1.90 to 5.69]) treatment groups when compared to placebo ($P = 0.228$ and $P = 0.499$, respectively). Only numerical reductions in nonvertebral (2/160 [1.3%] vs 3/144 [2.3%]), clinical fractures (5/160 [3.1%] vs 6/144 [1.2%]), MOF (1/160 [0.6%] vs 4/144 [2.8%]), or wrist fractures (1/160 [0.6%] vs 3/144 [2.1%]) were observed in participants treated with abaloparatide compared to placebo, respectively.

Change in BMD

In the participants from ACTIVE meeting ≥1 of the criteria for highest fracture risk, BMD gains from baseline were observed at the lumbar spine, total hip, and femoral neck of participants treated with abaloparatide or teriparatide compared with participants receiving placebo at all time points (6, 12, and 18 mo) ($P < 0.0001$ for all; Fig. 3). Bone mineral density gains were greater with abaloparatide treatment when compared with teriparatide at the lumbar spine (at 6 and 12 mo; $P < 0.05$), total hip, and femoral neck (at all time points; $P < 0.005$ for both).

Changes in BMD in participants at lower fracture risk were also greater with abaloparatide and teriparatide compared with placebo at the total hip, femoral neck, and lumbar spine at all time points ($P < 0.0001$ for abaloparatide; $P < 0.005$ for teriparatide). BMD changes with abaloparatide compared to teriparatide were greater ($P < 0.05$) at the total hip at 12 and 18 months and at the femoral neck at 12 months, but not at the lumbar spine at any time point.

Safety

In participants from ACTIVE with the highest fracture risk, rates of adverse events (AEs) were similar between treatment groups (Table 2). The most common treatment-emergent adverse events (TEAEs) were hypercalciuria (76 [11.5%]; 66 [9.8%]; 89 [13.0%]), dizziness (73 [11.0%]; 45 [6.7%]; 53 [7.7%]), and arthralgia (59 [8.9%]; 64 [9.5%]; 63 [9.2%]) for participants receiving abaloparatide, placebo, or teriparatide, respectively (Table 2). Safety findings were consistent with the overall study cohort.[12]

DISCUSSION

In a subpopulation of postmenopausal women in ACTIVE at highest risk for fracture based on criteria derived from professional society guidelines, 18 months of abaloparatide treatment resulted in a reduction in the risk of new vertebral fracture, clinical fracture, and MOF incidence compared to placebo. Additionally, gains in BMD from baseline were observed. Upon examination of new

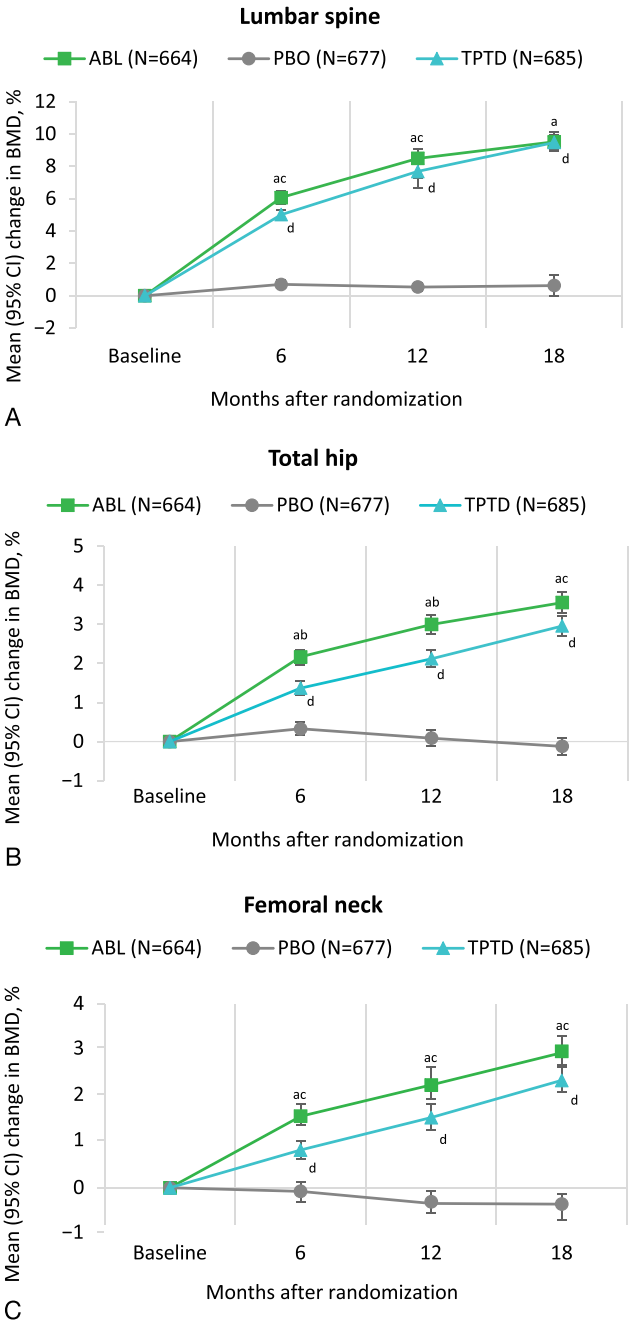

FIG. 3. Percent change in BMD at the **(A)** lumbar spine, **(B)** total hip, and **(C)** femoral neck in participants at highest risk for fracture at study months 6, 12, and 18, ITT Population. ITT population included all participants who were randomized into the study and received a study medication kit. Baseline change in BMD y-axes have different scales for lumbar spine versus total hip and femoral neck. *P* values were derived from contrast tests based on ANCOVA model fitted using only the data of the two treatment groups to be compared. Missing BMD data were imputed using the method of last observation carried forward. ABL, abaloparatide; ANCOVA, analysis of covariance; BMD, bone mineral density; CI, confidence interval; ITT, intent to treat; PBO, placebo; TPTD, teriparatide. [a]$P < 0.0001$ ABL vs PBO. [b]$P < 0.0001$ ABL vs TPTD. [c]$P < 0.05$ ABL vs TPTD. [d]$P < 0.0001$ TPTD vs PBO.

TABLE 2. Treatment-emergent adverse events, safety population[a]

Preferred term, n (%)	Abaloparatide (n = 662)	Placebo (n = 676)	Teriparatide (n = 685)
≥1 TEAE	587 (88.7)	595 (88.0)	610 (89.1)
Most frequent TEAEs (occurring in ≥5% of participants in any arm)			
Hypercalciuria	76 (11.5)	66 (9.8)	89 (13.0)
Dizziness	73 (11.0)	45 (6.7)	53 (7.7)
Arthralgia	59 (8.9)	64 (9.5)	63 (9.2)
Upper respiratory tract infection	59 (8.9)	59 (8.7)	67 (9.8)
Nausea	59 (8.9)	18 (2.7)	36 (5.3)
Back pain	58 (8.8)	71 (10.5)	50 (7.3)
Headache	54 (8.2)	41 (6.1)	45 (6.6)
Hypertension	49 (7.4)	46 (6.8)	38 (5.5)
Nasopharyngitis	43 (6.5)	55 (8.1)	46 (6.7)
Influenza	43 (6.5)	32 (4.7)	29 (4.2)
Palpitations	38 (5.7)	2 (0.3)	11 (1.6)
Urinary tract infection	37 (5.6)	34 (5.0)	30 (4.4)
Constipation	31 (4.7)	38 (5.6)	28 (4.1)
Pain in extremity	29 (4.4)	42 (6.2)	33 (4.8)
≥1 serious TEAE	60 (9.1)	77 (11.4)	70 (10.2)
≥1 AE leading to study discontinuation	65 (9.8)	47 (7.0)	46 (6.7)
≥1 AE leading to death	3 (0.5)	5 (0.7)	3 (0.4)

AE, adverse event; TEAE, treatment-emergent adverse event.
[a]The safety population included all participants who received at least one dose of study medication.

vertebral fracture incidence by baseline criteria subgroup (ie, recent fracture in the last 12 months or prevalent vertebral fracture, low T score, multiple fractures, or very high fracture probability by FRAX), both abaloparatide and teriparatide were associated with a reduction in fracture risk. Nonvertebral and clinical fracture risk reductions were only seen in the low T score (< -3.0) subgroup and were numerically lower for all other subgroups; however, the study was not sufficiently powered to assess these events in the high-risk subgroups.

Absolute fracture risk reduction is dependent on baseline risk, so individuals with high or very high fracture risk are expected to have more significant reductions with effective treatment than those with a lower baseline fracture risk. This is supported by a post hoc analysis of the ACTIVE study, which demonstrated a trend for greater risk reduction for MOF (69% [95% CI 38-85]) and clinical fractures (43% [9-64]; $P = 0.019$) among participants with higher baseline FRAX score treated with abaloparatide treatment compared to placebo.[15] Similar findings of greater efficacy among individuals with higher fracture risk probabilities have been reported for other osteoporosis treatments.[15]

In the ACTIVE study, participants treated with abaloparatide had an absolute risk reduction in new vertebral and nonvertebral fractures of 3.64% and 2.01%, respectively, when compared with placebo.[12] In the current study, the absolute risk reduction in new vertebral and nonvertebral fractures was 4.05% and 2.28%, respectively, in the participants with highest fracture risk treated with abaloparatide compared to placebo. For participants who did not meet highest fracture risk criteria, efficacy was better for those treated with abaloparatide when compared with placebo but was not statistically significant because of the small sample size.

Treatment-emergent AEs observed with abaloparatide were consistent with those observed in the overall ACTIVE population. In prior analyses, although abaloparatide treatment was associated with a transient increase in heart rate when compared to placebo, it did not increase the risk of serious cardiac AEs.[16]

There are some considerations for the study. Approximately 80% of the ACTIVE population met guideline criteria for being at very high risk for fractures. An indicator of high risk for future fractures is the occurrence of a vertebral fracture, even in the absence of a T score meeting the threshold for osteoporosis classification.[4] However, unless deliberate efforts are made to identify vertebral fractures through the utilization of imaging such as x-rays or vertebral fracture assessment, most will go undetected.[4] Although the AACE/ACE 2020 guidelines require a fracture to be recent for an individual to be considered at very high fracture risk and do not include prevalent vertebral fractures, this criterion was included in this study because morphometric vertebral fractures at baseline were accurately ascertained even though their recency could not be established. Additionally, The American Society for Bone and Mineral Research guidelines specify vertebral fractures as criteria to be considered at high risk of fracture when determining treatment for secondary fracture risk reduction.[5] Regardless of the definition, abaloparatide therapy reduces fracture risk across a range of fracture probabilities.

CONCLUSIONS

The findings of this subgroup analysis demonstrate that abaloparatide is effective in women from ACTIVE at highest fracture risk as defined based on criteria from several clinical practice guidelines.

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REFERENCES

1. Balasubramanian A, Zhang J, Chen L, et al. Risk of subsequent fracture after prior fracture among older women. *Osteoporos Int* 2019;30:79-92. doi: 10.1007/s00198-018-4732-1
2. Kanis JA, Cooper C, Rizzoli R, et al. Identification and management of patients at increased risk of osteoporotic fracture: outcomes of an ESCEO expert consensus meeting. *Osteoporos Int* 2017;28: 2023-2034. doi: 10.1007/s00198-017-4009-0
3. Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International

Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Arch Osteoporos* 2013;8:136. doi: 10.1007/s11657-013-0136-1
4. 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: 1-46. doi: 10.4158/GL-2020-0524SUPPL
5. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society* clinical practice guideline. *J Clin Endocrinol Metab* 2019;104:1595-1622. doi: 10. 1210/jc.2019-00221
6. Conley RB, Adib G, Adler RA, et al. Secondary fracture prevention: consensus clinical recommendations from a multi-stakeholder coalition. *J Bone Miner Res* 2020;35:36-52. doi: 10. 1002/jbmr.3877
7. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. *J Clin Endocrinol Metab* 2020;105:dgaa048. doi: 10.1210/clinem/dgaa048
8. Rentzeperi E, Pegiou S, Tsakiridis I, et al. Diagnosis and management of osteoporosis: a comprehensive review of guidelines. *Obstet Gynecol Surv* 2023;78:657-681. doi: 10.1097/OGX. 0000000000001181
9. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. *Menopause* 2021;28:973-997. doi: 10.1097/GME.0000000000001831
10. Cosman F, Lewiecki EM, Eastell R, et al. Goal-directed osteoporosis treatment: ASBMR/BHOF Task Force Position Statement 2024. *J Bone Miner Res* 2024;39:zjae119-zjae1405. doi: 10.1093/jbmr/ zjae119
11. Imamudeen N, Basheer A, Iqbal AM, Manjila N, Haroon NN, Manjila S. Management of osteoporosis and spinal fractures: contemporary guidelines and evolving paradigms. *Clin Med Res* 2022;20:95-106. doi: 10.3121/cmr.2021.1612
12. 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;316:722-733. doi: 10.1001/jama.2016.11136
13. 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: 141-149. doi: 10.1210/en.2015-1726
14. Tymlos. Prescribing information. Radius Health Inc; 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/ 208743lbl.pdf.Accessed June 12, 2024.
15. McCloskey EV, Johansson H, Oden A, et al. The effect of abaloparatide-SC on fracture risk is independent of baseline FRAX fracture probability: a post hoc analysis of the ACTIVE study. *J Bone Miner Res* 2017;32:1625-1631. doi: 10.1002/jbmr.3163
16. Cosman F, Peterson LR, Towler DA, Mitlak B, Wang Y, Cummings SR. Cardiovascular safety of abaloparatide in postmenopausal women with osteoporosis: analysis from the ACTIVE phase 3 trial. *J Clin Endocrinol Metab* 2020;105:3384-3395. doi: 10.1210/clinem/ dgaa450

