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# Effects of abaloparatide on bone mineral density and risk of fracture in postmenopausal women aged 80 years or older with osteoporosis

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**Abstract**

***Objective:*** Advanced age is an important risk factor for fracture. The Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) trial showed that subcutaneous abaloparatide increased bone mineral density (BMD) and reduced the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis. This study describes the effects of abaloparatide in the subgroup of women aged 80 or more years in ACTIVE.

***Methods:*** Post hoc analyses of BMD and fracture incidence in this subgroup of women who received abaloparatide or placebo in the 18-month, phase 3, double-blind, randomized controlled ACTIVE trial.

***Results:*** The mean ages of the women ≥80 years were 81.9 and 81.7 years in the placebo ($n = 43$) and abaloparatide ($n = 51$) groups, respectively. The increases in BMD from baseline to 18 months with abaloparatide treatment were 3.9% at the total hip ($P < 0.001$), 3.6% at the femoral neck ($P < 0.01$), and 12.1% at the lumbar spine ($P < 0.001$), and were similar to those observed in the overall population. Abaloparatide therapy was associated with numerical, but not statistically significant, reductions in the risk of vertebral and nonvertebral fractures in this subpopulation, compared with placebo. The proportion of participants reporting adverse events was similar between treatment groups and between the older subgroup and the overall population.

***Conclusion:*** Abaloparatide was effective in increasing BMD in the very elderly subgroup of ACTIVE, with a safety profile similar to that of the overall study population.

***Key Words:*** Abaloparatide – Bone mineral density – Older – Fracture risk – Osteoporosis – Postmenopausal women.



Osteoporosis is a disorder in which progressive bone loss damages skeletal architecture and impairs bone strength, resulting in increasing risk of fragility fracture.[1] The prevalence of osteoporosis and the risk of fracture increase progressively with advancing age, and the clinical consequences of vertebral and hip fractures are greater among older compared with younger women.[2-4] A myriad of skeletal and nonskeletal risk factors for fracture occur among very elderly women who are often frail and beset with other clinical problems. With our progressively aging population, there is strong interest in the effectiveness and safety of treatments in the oldest old (80 or more years of age).[5,6]

Abaloparatide is a 34-amino acid peptide that selectively binds to the parathyroid hormone receptor type 1 with higher selectivity for the RG versus $R^0$ conformation resulting in transient receptor signaling with a net anabolic effect.[7] In the multinational phase 3 Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE), treatment of women with postmenopausal osteoporosis with subcutaneous abaloparatide for 18 months significantly increased bone mineral density (BMD) and decreased the risk of vertebral and nonvertebral fractures compared with placebo, and was well tolerated.[8] In a preplanned subgroup analysis of ACTIVE, no interactions were observed between age at baseline as a function of three categories (<65, 65 to <75, and ≥75 y) and the treatment effect of abaloparatide on new morphometric vertebral fractures, nonvertebral fractures, or changes in BMD.[9] Because there is some controversy about the effectiveness and safety of treatments in the oldest old,[5,6] we

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describe in this report a post hoc analysis of the effects and safety of abaloparatide in the subgroup of participants aged 80 or more years in ACTIVE.

## PARTICIPANTS

### Participants and procedures

The multicenter ACTIVE study enrolled postmenopausal women, aged 49 to 86 years, with osteoporosis as defined by prior radiographic vertebral fracture or recent (within 5 y of enrollment) nonvertebral fracture with a BMD *T*-score $\leq -2.5$ and $> -5.0$ at the lumbar spine or femoral neck if aged $\leq 65$ years or $\leq -2.0$ and $> -5.0$ if aged $>65$ years.[8] For those aged $>65$ years, no prior fracture was required if the lumbar spine or femoral neck BMD *T*-score was $\leq -3.0$ and $> -5.0$. Other inclusion/exclusion criteria have been previously described.[8] As reported by Miller, women were screened after informed written consent was obtained and then randomized using a permuted-blocks design with a block size of 6 in a ratio of 1:1:1 to receive either double blinded daily injections of abaloparatide 80 μg or matching placebo, or open-label daily subcutaneous injections of teriparatide 20 μg for 18 months.[8] All participants received supplements of 500 to 1,000 mg/d elemental calcium and 400 to 800 IU vitamin D based on regional standard of care. The endpoints were assessed as previously described,[8] including the primary endpoint of the incidence of new vertebral fractures from baseline to 18 months in participants treated with abaloparatide compared with placebo. Nonvertebral fractures, a secondary endpoint, were initially self-reported and then verified from source documents and excluded those of the spine, sternum, patella, toes, fingers, skull, and face and fractures associated with high trauma. Study oversight was performed and safety was assessed as previously described.[8] Laboratory and radiological analyses were conducted by individuals who were blinded to all treatments.

### Statistical analyses

The primary and key secondary endpoints in ACTIVE were included in these post hoc analyses of a subset of women $\geq 80$ years of age in the abaloparatide and placebo arms. Results for the overall population in the abaloparatide and placebo arms are included for comparison. The intent-to-treat (ITT) population included all participants who were randomized to receive study medication and was used for all efficacy analyses except for those of vertebral fracture. The modified ITT population included all ITT patients who received both pretreatment and postbaseline spine radiographs and the radiographs from this population were used for analysis of new morphometric vertebral fractures. The safety population included all women who received one or more doses of study medication. The percent change in BMD from baseline to each study visit was compared using a mixed-effect repeated measures model. Relative risk ratios for new vertebral fractures were calculated using the Fisher's exact test. Time to nonvertebral fracture was compared using the log-rank test in all participants through the entire observational period of 19 months (18 mo of treatment and 1 mo of follow-up), as previously described.[8] Hazard ratios for nonvertebral fractures were calculated using the Cox proportional hazards model. As this was an exploratory analysis, the *P* values were not adjusted for multiple comparisons and were considered significant if $<0.05$.

## RESULTS

Among the 1,645 women in the abaloparatide and placebo-blinded arms of the ACTIVE trial, 94 (5.7%) were aged 80 years or older. Baseline characteristics for these very elderly participants and the overall population are presented in Table 1. The mean ages of the women in the very elderly subgroup were 81.9 and 81.7 years in the placebo and abaloparatide groups, respectively, and these women were approximately 13 years older than those in the overall population at baseline. As expected, the BMD *T*-scores at the total hip and femoral neck were slightly lower in the very elderly age cohort than in the overall population. Consistent with the inclusion criterion for women $>65$ years of age, fewer very elderly women reported having a nonvertebral fracture within 5 years before enrollment. A larger proportion of women in

**TABLE 1.** *Demographics and baseline characteristics, ACTIVE trial*

| | Placebo | | Abaloparatide | |
|---|---|---|---|---|
| Characteristic | All, $n=821$ | ≥80 y, $n=43$ | All, $n=824$ | ≥80 y, $n=51$ |
| Age, mean y (SD) | 68.7 (6.5) | 81.9 (1.5) | 68.9 (6.5) | 81.7 (1.4) |
| BMI, mean kg/m$^2$ (SD) | 25.1 (3.6) | 25.2 (3.8) | 25.0 (3.5) | 24.7 (3.3) |
| Race, *n* (%) | | | | |
| White | 655 (79.8) | 27 (62.8) | 663 (80.5) | 34 (66.7) |
| Asian | 131 (16.0) | 14 (32.6) | 128 (15.5) | 13 (25.5) |
| Black or African-American | 23 (2.8) | 2 (4.7) | 26 (3.2) | 4 (7.8) |
| Other | 12 (1.5) | 0 | 7 (0.8) | 0 |
| Hispanic or Latino, *n* (%) | 199 (24.2) | 18 (41.9) | 199 (24.2) | 21 (41.2) |
| BMD *T*-score, mean (SD) | | | | |
| Total hip | −1.9 (0.8) | −2.4 (0.7) | −1.9 (0.7) | −2.2 (0.8) |
| Femoral neck | −2.2 (0.7) | −2.6 (0.6) | −2.2 (0.6) | −2.5 (0.6) |
| Lumbar spine | −2.9 (0.8) | −3.0 (0.9) | −2.9 (0.9) | −2.6 (1.3) |
| Prevalent vertebral fracture at baseline, *n* (%) | 188 (22.9) | 9 (20.9) | 177 (21.5) | 19 (37.3) |
| Prior nonvertebral fracture within 5 y of study day 1, *n* (%) | 266 (32.4) | 8 (18.6) | 248 (30.1) | 7 (13.7) |

Values for overall population from reference 8.
ACTIVE, Abaloparatide Comparator Trial In Vertebral Endpoints; BMD, bone mineral density; BMI, body mass index.

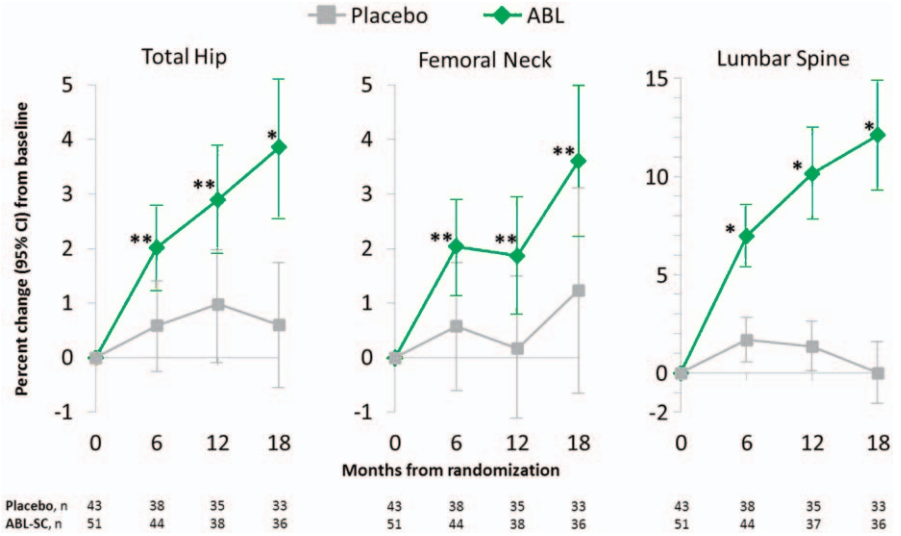


**FIG. 1.** Mean percent change (95% CI) in BMD at total hip, femoral neck, and lumbar spine among women aged >80 years. $^{*}P < 0.001$ versus placebo; $^{**}P < 0.01$ versus placebo. ABL, abaloparatide.

the abaloparatide very elderly group had prevalent vertebral fractures at baseline, but other baseline characteristics were generally matched between treatment groups, and none of the differences were statistically significant.

Changes in BMD over the 18-month treatment period are shown in Figure 1. In this very elderly age group treated with abaloparatide, the increase in BMD at the total hip was significant at the first postbaseline measurement at 6 months (2.0% [95% CI, 1.2%-2.8%]; $P < 0.01$ compared with placebo). After 18 months of treatment with abaloparatide, the increases in BMD from baseline were 3.9% [95% CI, 2.5% - 5.2%], $P < 0.001$ compared with placebo at the total hip; 3.6% [95% CI, 2.2%-5.0%], $P < 0.01$ compared with placebo at the femoral neck; and 12.1% [95% CI, 9.3%-14.9%], $P < 0.001$ compared with placebo at the lumbar spine. These increases in BMD from baseline in the women aged ≥80 years were similar to those reported for the overall population, with BMD increases from baseline at 6 months of 2.3% at the total hip, and at 18 months of 4.18% at the total hip, 3.6% at the femoral neck, 11.2% at the lumbar spine.[8]

The number of fractures was small in the very elderly age cohort, consisting of two new vertebral and two nonvertebral fractures in the very elderly placebo group, and zero and one, respectively, in the very elderly abaloparatide group. The numerical reductions in fracture risk with abaloparatide therapy, although not statistically significant, are consistent with the effectiveness of abaloparatide in reducing vertebral and nonvertebral fractures in the overall ACTIVE population.

The proportions of participants reporting adverse events were similar between treatment groups and between the very elderly age cohorts and the overall population (Table 2). As expected in an older population, the proportion of women 80 years and older who reported serious adverse events was higher than in the entire study cohort but did not differ between the abaloparatide and placebo groups. The overall discontinuation rate for the very elderly age cohort (30.9%) was higher than for the entire study cohort (24.4%).

## DISCUSSION

In the subgroup of women aged 80 years or older, abaloparatide significantly increased BMD of the total hip, femoral neck, and lumbar spine, with increments of similar magnitude to those seen in the overall study. The numerical reductions in the risk of vertebral and nonvertebral fracture with abaloparatide were also similar to the effects described in the entire ACTIVE trial, albeit with these analyses limited by the very small number of fracture events in this very elderly subgroup. Tolerability and safety were also similar in the very elderly cohort versus the entire ACTIVE cohort.

Older age is a consistent risk factor for both falls and for osteoporosis as diagnosed by low BMD, both of which are important and independent risk factors for fracture.[10,11] Women aged 75 years and older with hip *T*-score values consistent with osteoporosis are at higher risk of fracture than are women of the same age with higher BMD values, although it seems that the contribution of low BMD to fracture risk is less among older compared with younger postmenopausal women, perhaps related to the accumulation of fall-related risk factors with advancing age.[12] Prevalence of vertebral fracture is also higher in the elderly population, regardless of BMD.[13]

The effectiveness of osteoporosis drugs in older women was initially addressed in the risedronate hip fracture trial in which risedronate significantly decreased the risk of hip fracture in postmenopausal women aged 70 to 79 years with low BMD.[14] In a group of women at least 80 years old enrolled primarily on the basis of fall-related risk factors, the 20% reduction in hip fracture risk was, however, not statistically significant. Subsequently, in a post hoc analysis of the subgroup of participants in this study who were at least

**TABLE 2.** *Safety and adverse events, ACTIVE trial*

| Event, *n* (%) | Placebo | | Abaloparatide | |
|---|---|---|---|---|
| | All, $n = 820$ | ≥80 y, $n = 43$ | All, $n = 822$ | ≥80 y, $n = 51$ |
| ≥1 TEAE | 718 (87.6) | 34 (79.1) | 735 (89.4) | 44 (86.3) |
| ≥1 Serious TEAE | 90 (11.0) | 8 (18.6) | 80 (9.7) | 11 (21.6) |
| ≥1 TEAE leading to death[a] | 5 (0.6) | 0 | 3 (0.4) | 3 (5.9) |
| ≥1 TEAE leading to discontinuation | 50 (6.1) | 1 (2.3) | 81 (9.9) | 6 (11.8) |
| Common TEAEs[b] | | | | |
| Upper respiratory tract infection | 63 (7.7) | 6 (14.0) | 68 (8.3) | 10 (19.6) |
| Dizziness | 50 (6.1) | 5 (11.6) | 82 (10.0) | 7 (13.7) |
| Hypertension | 54 (6.6) | 3 (7.0) | 59 (7.2) | 7 (13.7) |
| Nasopharyngitis | 66 (8.0) | 2 (4.7) | 48 (5.8) | 4 (7.8) |
| Influenza | 39 (4.8) | 1 (2.3) | 52 (6.3) | 4 (7.8) |
| Muscle spasms | 16 (2.0) | 1 (2.3) | 22 (2.7) | 4 (7.8) |
| Osteoarthritis | 31 (3.8) | 1 (2.3) | 34 (4.1) | 4 (7.8) |
| Pain in extremity | 49 (6.0) | 3 (7.0) | 40 (4.9) | 3 (5.9) |
| Hypercalciuria | 74 (9.0) | 4 (9.3) | 93 (11.3) | 3 (5.9) |
| Urinary tract infection | 38 (4.6) | 4 (9.3) | 43 (5.2) | 2 (3.9) |
| Back pain | 82 (10.0) | 4 (9.3) | 70 (8.5) | 2 (3.9) |
| Anemia | 15 (1.8) | 3 (7.0) | 23 (2.8) | 2 (3.9) |
| Bronchitis | 20 (2.4) | 3 (7.0) | 19 (2.3) | 2 (3.9) |
| Constipation | 42 (5.1) | 3 (7.0) | 37 (4.5) | 1 (2.0) |
| Arthralgia | 80 (9.8) | 5 (11.6) | 71 (8.6) | 0 |
| Hypertriglyceridemia | 21 (2.6) | 3 (7.0) | 20 (2.4) | 0 |

Values for overall population from reference 6 and data on file.
TEAE, treatment-emergent adverse event.
[a]Causes of death among the overall population in the placebo group: bowel cancer, intestinal obstruction, myocardial infarction, dissecting aneurysm of the aorta, sudden death; in the abaloparatide group: sepsis, bronchiectasis, ischemic heart disease.
[b]Occurring in ≥5% in either of the ≥80 years treatment groups.

80 years old with osteoporosis by BMD or prevalent vertebral fracture criteria, risedronate statistically significantly reduced the risk of hip fracture.[15] In addition, in a post hoc analysis of pooled data from the phase 3 risedronate fracture endpoint trials, risedronate reduced the risk of vertebral fracture in participants who were at least 80 years old with osteoporosis or at least one prevalent vertebral fracture.[16] A retrospective subgroup analysis in men and women with osteoporosis ≥80 years treated with teriparatide demonstrated similar effects of therapy on BMD compared with treatment of women <80 years.[17] In a post hoc analysis of the phase 3 trial with zoledronic acid, there were significant reductions in clinical vertebral and nonvertebral fractures in postmenopausal women with osteoporosis ≥75 years of age.[18] In a post hoc analysis of a phase 3 study, denosumab significantly reduced the risk of hip fracture in a subset of postmenopausal women aged 75 years or older at high risk for fracture.[19] Our results with abaloparatide presented here are consistent with these subgroup analyses.

The strength of these analyses is the clinically important subgroup of very elderly women studied. The limitations include the post hoc nature of the analyses, as well as those limitations related to subgroup analyses including lack of adjustment for multiple comparisons, possible confounding as a result of the lack of stratification by age in the original randomization, and the small number of fracture events.

## CONCLUSIONS

In the subgroup of women aged 80 years or older, abaloparatide therapy was associated with significantly increased BMD of the lumbar spine and proximal femur, numerically fewer vertebral and nonvertebral fractures, and no differences in the safety profile. These findings are consistent with efficacy of abaloparatide in the very elderly comparable to that in the general older population. As life expectancy is increasing and a growing proportion of individuals in the next 30 years will be in the at risk older category, it will be important to further develop such therapeutic options that clearly reduce fractures in the very old if we hope to make a substantial impact on disability, loss of independence, and mortality from complications of osteoporosis.

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