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Bone mineral density response rates are greater in patients treated with abaloparatide compared with those treated with placebo or teriparatide: Results from the ACTIVE phase 3 trial

P.D. Miller[a], G. Hattersley[b,*], E. Lau[c], L.A. Fitzpatrick[b], A.G. Harris[d], G.C. Williams[b], M.-Y. Hu[b], B.J. Riis[e], L. Russo[f], C. Christiansen[e]

[a] Colorado Center for Bone Research, Lakewood, CO, United States of America
[b] Radius Health, Inc., Waltham, MA, United States of America
[c] Center for Health & Medical Research, Hong Kong, People's Republic of China
[d] NYU Langone School of Medicine, New York, NY, United States of America
[e] Nordic Bioscience, Copenhagen, Denmark
[f] Center for Clinical and Basic Research, Rio de Janeiro, Brazil

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ABSTRACT

Background: Abaloparatide is a 34–amino acid peptide that selectively binds to the RG conformation of the parathyroid hormone receptor type 1. It was developed for the treatment of women with postmenopausal osteoporosis at high risk of fracture. In ACTIVE, an 18-month phase 3 study (NCT01343004), abaloparatide increased bone mineral density (BMD), decreased the risk of vertebral and nonvertebral fractures compared with placebo, and decreased the risk of major osteoporotic fractures compared with placebo and teriparatide. Here, we report a prospective, exploratory BMD responder analysis from ACTIVE.

Methods: Proportions of patients experiencing BMD gains from baseline of > 0%, > 3%, and > 6% at the total hip, femoral neck, and lumbar spine at 6, 12, and 18 months of treatment were compared among the placebo, abaloparatide, and teriparatide groups in ACTIVE. Responders were defined prospectively as patients experiencing BMD gains at all 3 anatomic sites.

Results: At months 6, 12, and 18, there were significantly more > 3% BMD responders in the abaloparatide group compared with placebo and teriparatide: month 6, 19.1% vs 0.9% for placebo and 6.5% for teriparatide; month 12, 33.2% vs 1.5% and 19.8%; month 18, 44.5% vs 1.9% and 32.0% ($P < 0.001$ for all comparisons of abaloparatide to placebo and to teriparatide). Findings were similar for the > 0% and > 6% responder thresholds.

Conclusions: In postmenopausal women with osteoporosis, a significantly greater proportion of patients treated with abaloparatide experienced increases in BMD than did those treated with placebo or teriparatide.

1. Introduction

Osteoporotic fractures are a major cause of morbidity and mortality in our aging population [1]. There are now a number of effective treatments available for reducing the risk of fracture. These include antiresorptive agents, which act primarily by reducing bone resorption and secondarily reducing bone formation, and anabolic agents, which act primarily to increase bone formation [2–4]. A rapid response to osteoporosis treatment may be important, particularly in patients with recent fractures who are at high risk for subsequent fracture [5]. Although the main goal of osteoporosis treatment is reduction in the risk of fractures, changes in bone mineral density (BMD) are commonly used to monitor effects of treatment [1].

Abaloparatide is a 34–amino acid peptide that selectively binds to the RG conformation of the parathyroid hormone (PTH) receptor type 1 and demonstrates a potent effect on bone anabolic activity resulting in lower resorptive and calcemic responses compared with teriparatide [6–8]. In a 24-week phase 2 study of 222 postmenopausal women with osteoporosis, abaloparatide 80 μg/d was associated with significantly greater increases in BMD at the total hip, femoral neck, and lumbar spine, compared with placebo [6]. The increase in total hip BMD of 2.6% with abaloparatide 80 μg/d was significantly greater than with

* Corresponding author at: Radius Health Inc., 950 Winter St, Waltham, MA 02451, United States of America.
E-mail address: ghattersley@radiuspharm.com (G. Hattersley).

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teriparatide (0.5%; $P = 0.006$). A post hoc analysis demonstrated that more women treated with abaloparatide had a > 3% BMD gain at the total hip (37%) than did those treated with teriparatide (16%, $P < 0.02$) or placebo (15%, $P < 0.04$). The 3% threshold was chosen for this phase 2 study to represent least significant change (LSC) to conform with prior responder analyses [6,9–13].

In the 18-month phase 3 Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE, NCT01343004), abaloparatide increased BMD and decreased the risk of vertebral and nonvertebral fractures compared with placebo. In addition to blinded placebo and abaloparatide arms, ACTIVE included an open-label teriparatide arm. Abaloparatide increased BMD at nonvertebral sites and decreased the risk of major osteoporotic fractures compared with teriparatide [7].

To determine if postmenopausal women with osteoporosis treated with an 18-month course of abaloparatide were more likely to respond to treatment with BMD gains than were those treated with either placebo or teriparatide, a prospectively planned responder analysis was performed in ACTIVE. Three responder thresholds were explored: > 3%, representing a recognized LSC; > 0%, representing any positive change; and > 6%, representing a more robust threshold of positive change.

2. Methods

2.1. Study patients

ACTIVE enrolled 2463 postmenopausal women with osteoporosis and randomized them to receive either blinded daily injections of abaloparatide 80 μg or matching placebo or open-label daily injections of teriparatide 20 μg for 18 months. Inclusion and exclusion criteria and study design and methodology have been described in detail by Miller et al. [7].

2.2. Responder analysis endpoints

The responder analysis was a prespecified exploratory endpoint comparing the proportion of patients experiencing BMD gains of > 0%, > 3%, and > 6% from baseline at the total hip, femoral neck, and lumbar spine at 6, 12, and 18 months. A responder was defined as a patient with a gain in BMD at all 3 anatomic sites. The > 3% threshold was chosen based on dual-energy x-ray absorptiometry (DXA) scanner precision of approximately 1% corresponding to the LSC in BMD at the 95% confidence limits of 3% and to conform with responder analyses performed in other studies of drugs to treat osteoporosis [6,9–14]. BMD was measured by DXA on approved scanners (Hologic, Bedford, MA, or GE Healthcare Lunar, Madison WI), and for each patient, the same scanner was used for all evaluations of BMD. If a scanner was changed during the course of the study, adjustments were made to correct differences between the old and new scanner (Bioclinica-Synarc, Newark, CA, USA).

2.3. Statistical analyses

The responder analysis included all patients in ACTIVE who had both a baseline BMD and a post-baseline BMD determination at the 18-month visit within the intent-to-treat (ITT) population. Patients who had missing BMD results at any of the 3 anatomic sites (total hip, femoral neck, lumbar spine) were not included in the “all-anatomic-sites” analysis, and no imputation of missing data was performed. BMD percent increases of > 0%, > 3%, and > 6% at all 3 anatomic sites were used as thresholds of response. BMD percent increases of > 0%, > 3%, and > 6% were also calculated for individual anatomic sites, and included all patients with a baseline and post-baseline assessment at the respective anatomic site.

The χ^2 test was used to explore the differences in the proportion of responders between 2 treatment groups compared at each visit for each degree of response. The Fisher's exact test was used if the number of responders was fewer than 5 in any of the 3 treatment groups. No multiplicity adjustments to the P values were used.

Table 1
Demographics and baseline characteristics of ACTIVE study participants included in responder analysis[a]

	Placebo (n = 650)	Abaloparatide (n = 613)	Teriparatide (n = 660)
Age, mean (SD), years	68.6 (6.3)	68.7 (6.6)	68.5 (6.3)
Time since menopause, mean (SD), years	19.7 (7.9)	20.3 (8.2)	20.0 (8.0)
Weight, mean (SD), kg	61.2 (10.0)	61.2 (9.9)	61.1 (10.2)
Body mass index, mean (SD)	25.0 (3.5)	25.0 (3.5)	25.1 (3.6)
Race, n (%)			
White	507 (78.0)	481 (78.5)	513 (77.7)
Asian	115 (17.7)	106 (17.3)	122 (18.5)
Black or African American	18 (2.8)	20 (3.3)	13 (2.0)
Other	10 (1.5)	6 (1.0)	12 (1.8)
BMD T-score, mean (SD)			
Total hip	−1.9 (0.77)	−1.9 (0.73)	−1.8 (0.75)
Femoral neck	−2.2 (0.68)	−2.1 (0.63)	−2.1 (0.66)
Lumbar spine	−2.9 (0.83)	−2.9 (0.88)	−2.9 (0.89)
Prevalent vertebral fracture, n (%)	152 (23.4)	132 (21.5)	181 (27.4)

Abbreviations: BMD, bone mineral density; SD, standard deviation.
[a] Includes 1923 patients in intent-to-treat population who had BMD determinations at all 3 anatomic sites at baseline and at 18 months (78% of the ACTIVE ITT population).

3. Results

3.1. Patient disposition and demographics

Patient disposition and demographic characteristics in ACTIVE have been previously published [7]. Briefly, 2463 women were enrolled at 28 centers in 10 countries and randomized to receive abaloparatide (n = 824), placebo (n = 821), or teriparatide (n = 818). The mean age was 68.8 years, and baseline mean femoral neck BMD T-score was −2.1. Baseline demographic characteristics were similar among treatment arms. A total of 1923 (78%) patients had BMD determinations at all 3 anatomic sites at baseline and at 18 months and are included in this analysis. Baseline characteristics for these patients (Table 1) were similar to those of the overall study population.

3.2. BMD responders at all 3 anatomic sites (total hip, femoral neck, lumbar spine)

Fig. 1 shows the proportion of patients in each treatment group who were all-anatomic-site responders at each treatment visit (months 6, 12, and 18). At each visit, a significantly greater proportion of patients treated with abaloparatide were responders at each of the thresholds (> 0%, > 3%, and > 6%) compared with both placebo and teriparatide treatment. For example, applying a > 3% threshold, 116 (19.1%) patients treated with abaloparatide had increases in BMD at all 3 anatomic sites compared with 6 (0.9%) for placebo and 43 (6.5%) for teriparatide at 6 months. Corresponding values at month 12 were 203 (33.2%) abaloparatide patients compared with 10 (1.5%) placebo and 130 (19.8%) teriparatide patients, and at month 18, there were 273 (44.5%) abaloparatide patients compared with 12 (1.8%) placebo and 211 (32.0%) teriparatide patients who met the LSC. At all timepoints, significantly more patients responded with a > 3% increase at all 3 anatomic sites to abaloparatide than to placebo or to teriparatide ($P < 0.001$).

At 6% threshold, findings were similar: at 6 months, 14 (2.3%)

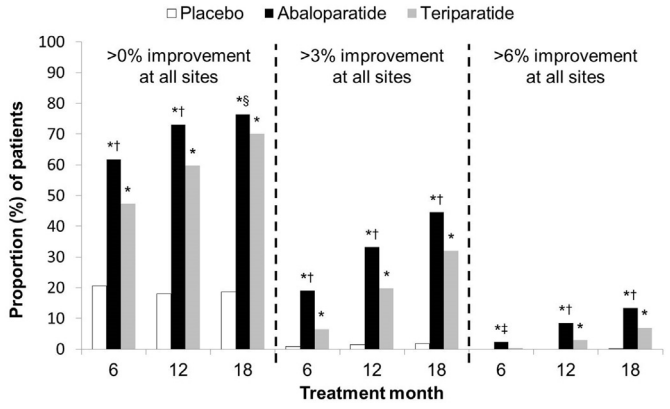

Fig. 1. Proportion of responders.
Response rates for placebo, abaloparatide, and teriparatide defined as BMD increases > 0%, > 3%, and > 6% from baseline at all 3 anatomic sites (total hip, femoral neck, lumbar spine). The analyses were performed at 6, 12, and 18 months of the ACTIVE study. The numbers of evaluable patients were placebo, n = 650 at months 6, 12, 18; abaloparatide, n = 609 at month 6, n = 612 at month 12, and n = 613 at month 18; teriparatide, n = 657 at months 6 and 12 and n = 660 at month 18.
*$P < 0.001$ abaloparatide or teriparatide vs placebo; †$P < 0.001$ abaloparatide vs teriparatide; ‡$P < 0.01$ abaloparatide vs teriparatide; §$P < 0.05$ abaloparatide vs teriparatide.
Abbreviation: BMD, bone mineral density.

abaloparatide patients had a > 6% in BMD at all 3 anatomic sites compared with 0 placebo and 2 (0.3%) teriparatide patients. At 12 months, 52 (8.5%) abaloparatide patients, 0 placebo, and 19 (2.9%) teriparatide patients were responders, and at 18 months, 82 (13.4%) abaloparatide, 1 placebo (0.2%), and 46 (7.0%) teriparatide patients were responders. At all 3 timepoints, significantly more patients responded to abaloparatide > 6% than to placebo or to teriparatide ($P < 0.001$ for all comparisons between abaloparatide and teriparatide except for $P = 0.002$ at 6 months).

3.3. BMD increases at individual anatomic sites

Fig. 2 displays the proportion of patients who met each BMD increase threshold (> 0%, > 3%, and > 6%) at each anatomic site (total hip, femoral neck, and lumbar spine) at 6, 12, and 18 months. Significantly greater proportions of patients treated with abaloparatide met each BMD increase threshold at each anatomic site and each timepoint than did patients who received placebo (all $P < 0.001$).

At the total hip and femoral neck, there were significantly more patients with > 3% increases at each timepoint among the abaloparatide group than among the teriparatide group. At the total hip, significantly more patients met the more robust increase threshold of > 6% with abaloparatide than with teriparatide at each timepoint: 7.9% vs 3.3% at 6 months; 19.0% vs 10.5% at 12 months; and 26.3% vs 18.5% at 18 months, all $P < 0.001$. At the femoral neck, the proportions of patients meeting the > 6% threshold with abaloparatide vs teriparatide were 9.7% vs 3.8% at 6 months; 16.1% vs 9.9% at 12 months; and 23.1% vs 15.0% at 18 months, all $P < 0.001$.

At the lumbar spine, there were significantly more patients who met all 3 BMD increase thresholds at 6 months among those treated with abaloparatide than with teriparatide (all $P \leq 0.003$). There were also significantly more patients meeting the > 6% threshold with abaloparatide vs teriparatide at 12 months ($P = 0.002$). All other comparisons between abaloparatide and teriparatide for lumbar spine BMD were not significant.

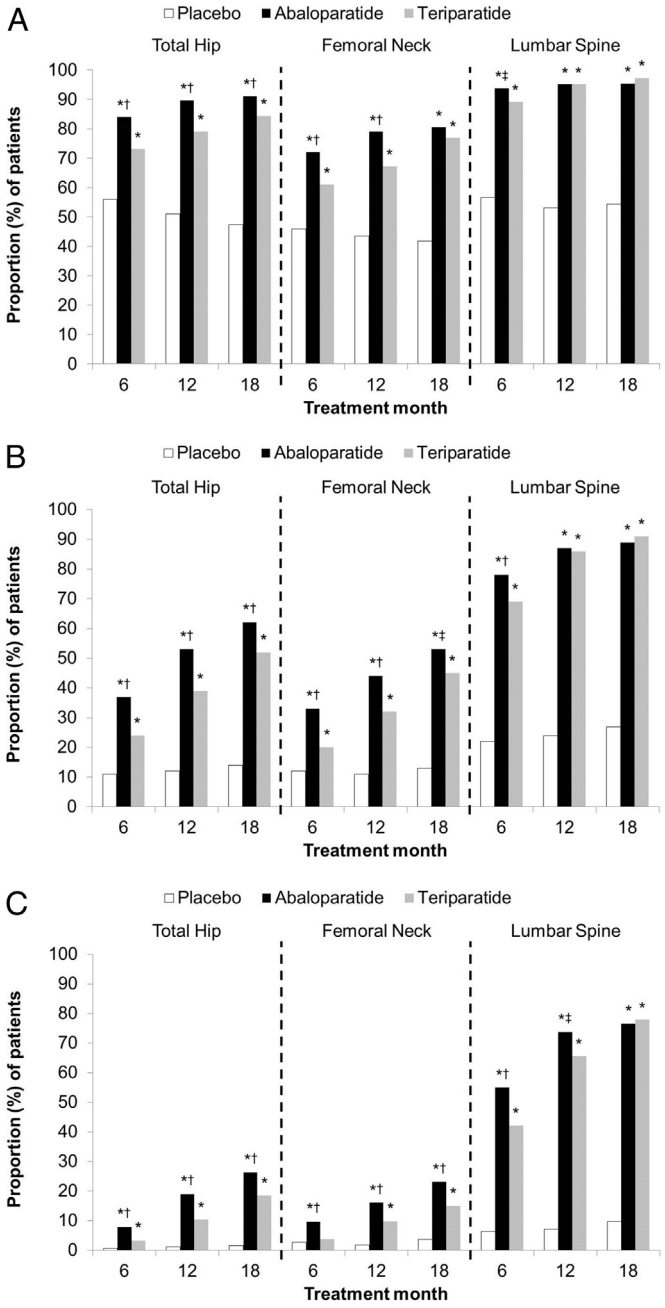

Fig. 2. Proportions of patients with each of 3 levels of BMD change at each anatomic site by timepoint measured.
Proportion of patients§ who achieved > 0% (panel A), > 3% (panel B), and > 6% (panel C) BMD increase at total hip, femoral neck, and lumbar spine, by treatment month.
*$P < 0.001$ abaloparatide or teriparatide vs placebo; †$P < 0.001$ abaloparatide vs teriparatide; ‡$P < 0.01$ abaloparatide vs teriparatide.
§For all panels: placebo, n = 651 for total hip and femoral neck, and n = 650 for lumbar spine; abaloparatide, n = 615 for total hip and femoral neck except at month 6 (n = 611), and n = 614, 616, and 617 for lumbar spine at months 6, 12, and 18; teriparatide, n = 660 for total hip and femoral neck except at month 6 (n = 658), and n = 663, 662, and 665 for lumbar spine at months 6, 12, and 18.
Abbreviation: BMD, bone mineral density.

4. Discussion

In this analysis, more patients in the abaloparatide group met the definition of a responder, defined prospectively as patients who

experienced increases in BMD at all 3 anatomic sites. Based on this definition, a greater proportion of responders was observed for abaloparatide compared with placebo and teriparatide at all thresholds of response (> 0%, > 3%, and > 6%), and at all time points (6, 12, and 18 months) compared with both placebo and with teriparatide (Fig. 1).

Hip fractures are an immense burden on the individuals who suffer them, their families and caregivers, and society, and they are associated with excess mortality and increased risk of future fractures [1]. In our analysis, there were significantly more patients in the abaloparatide group who had increases in total hip BMD for each threshold at 6, 12, and 18 months than there were in the placebo or teriparatide groups. Furthermore, our analysis shows that more abaloparatide patients had a BMD increase at the more robust > 6% response threshold compared with teriparatide at the total hip at each timepoint.

Response rates ≥3%, a common threshold for LSC analyses [6,9–14], have been previously described at the individual anatomic site of the hip for teriparatide compared with placebo and with alendronate in an analysis of 3 trials by Gallagher et al. [13]. Two of the trials described by Gallagher studied 20 μg/d teriparatide, the dosage of teriparatide used in ACTIVE. In The Fracture Prevention Trial, which included 1637 total patients, the BMD response rate for teriparatide 20 μg/d among 197 patients who had hip BMD measurement at baseline, 3, 6, 12, and 18 month was 32% (n = 62) at 12 months and 47% (n = 93) at 18 months. Likewise, in a comparator trial vs alendronate, among 68 patients treated with teriparatide 20 μg/d and 71 treated with alendronate, the response rate with teriparatide at the hip was 57% (n = 39) at 18 months vs 58% (n = 42) for alendronate [13]. In both these trials, the ≥3% response rate with teriparatide 20 μg/d was similar to the response rate for teriparatide 20 μg/d in ACTIVE and less than the response rate obtained with abaloparatide in ACTIVE.

A potential limitation of these analyses is their exploratory nature; further study is required to confirm between-group comparisons as well as to confirm their clinical relevance with respect to correlations with fracture risk reduction. In addition, the majority of patients did not achieve a 3% gain in BMD at all sites.

5. Conclusion

More women were all-anatomic-sites responders to abaloparatide than to teriparatide. There were more total hip BMD responders to abaloparatide than to teriparatide at all increase thresholds at all timepoints, including at the earliest timepoint measured, 6 months. The early increase in BMD seen with abaloparatide and the greater proportion of BMD responders at 6 months compared with teriparatide is consistent with the early nonvertebral fracture risk reduction seen with abaloparatide treatment in ACTIVE, although larger studies and formal correlation analyses would be required to confirm these findings.

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