Response rates for hip, femoral neck, and lumbar spine bone mineral density in patients treated with abaloparatide followed by alendronate: Results from phase 3 ACTIVExtend

Chad L. Deal[a,*], Bruce H. Mitlak[b], Yamei Wang[b], Lorraine A. Fitzpatrick[b], Paul D. Miller[c]

[a] Cleveland Clinic, Cleveland, OH, USA
[b] Radius Health, Inc., Waltham, MA, USA
[c] Colorado Center for Bone Research at Panorama Orthopedics & Spine Center, Golden, CO, USA

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ABSTRACT

Abaloparatide is a selective activator of the parathyroid hormone type 1 receptor signaling pathway that favors the stimulation of bone formation. Here, we report a prospective, exploratory analysis of bone mineral density (BMD) response rates comparing sequential abaloparatide/alendronate vs placebo/alendronate across the ACTIVE and ACTIVExtend studies. BMD was measured at the lumbar spine, total hip, and femoral neck from the beginning of ACTIVE to the end of ACTIVExtend (18 months of abaloparatide or placebo followed by about 1 month for re-consent, followed by 24 months of alendronate treatment for a total of 43 months). Responders were defined as those patients who had improvements in BMD at 3 anatomic sites—the lumbar spine, total hip, and femoral neck. Three response thresholds, > 0%, > 3%, and > 6%, were evaluated. Five hundred fifty-eight patients in the abaloparatide/alendronate group and 581 patients in the placebo/alendronate group from ACTIVExtend were included in the analysis. At Month 43, a significantly greater proportion of those in the abaloparatide/alendronate group compared with the placebo/alendronate group responded with BMD changes from ACTIVE baseline of > 0%, > 3%, and > 6% at all 3 anatomic sites (p < 0.001 for each comparison). At the > 3% threshold, 60.7% (307/506) vs 24.0% (121/505) of patients experienced BMD increases at all 3 sites in the abaloparatide/alendronate vs placebo/alendronate groups, respectively (p < 0.001). A significantly greater proportion of the abaloparatide/alendronate group experienced BMD increases of > 0%, > 3%, and > 6% at each individual anatomic site compared with the placebo/alendronate group at 43 months (p < 0.001). Additionally, at each visit in ACTIVExtend, there was a significantly greater proportion of patients in the abaloparatide/alendronate group above the 3% threshold at each anatomic site compared with the placebo/alendronate group. Results are consistent with the significant BMD response with abaloparatide vs placebo observed in ACTIVE and with the continued fracture risk reduction with sequential abaloparatide/alendronate compared with placebo/alendronate treatment observed in ACTIVE through ACTIVExtend.

1. Introduction

Fracture prevention is the goal of osteoporosis treatment. Each osteoporotic fracture has a substantial impact on quality of life, morbidity, and mortality, and the incidence of such fractures is rising in the aging populations of developed countries (Marrinan et al., 2015; Watts, 2014; Cosman et al., 2014; Bliuc et al., 2015; Burge et al., 2007; Hernlund et al., 2013).

Abaloparatide is a selective (for the RG conformation) activator of

the parathyroid hormone 1 receptor (PTH1R) signaling pathway (Hattersley et al., 2016). Signaling through the RG conformation results in less stimulation of resorption than does signaling through the R^0 conformation. In preclinical studies, abaloparatide demonstrated significant increases in BMD, restoration of bone microarchitecture, and increased bone strength (Varela et al., 2017a; Varela et al., 2017b; Doyle et al., 2018). ACTIVE (NCT01343004) was a multicenter, multinational, randomized, double-blind, placebo and active-controlled phase 3 trial of abaloparatide in women with postmenopausal

osteoporosis (Miller et al., 2016). A total of 2463 patients were randomly assigned to 18 months of daily subcutaneous abaloparatide, matching placebo, or open-label teriparatide (1:1:1) (Miller et al., 2016). Women with postmenopausal osteoporosis treated with abaloparatide demonstrated significant BMD increases at the lumbar spine, total hip, and femoral neck. After 18 months of treatment with abaloparatide, there were significant reductions in risk of vertebral, nonvertebral, clinical, and major osteoporotic fractures compared with placebo (Miller et al., 2016). At the conclusion of ACTIVE, patients assigned to receive abaloparatide or placebo were offered enrollment in an extension study, ACTIVExtend (NCT01657162). After about 1 month to obtain consent, patients received alendronate 70 mg weekly for 24 months (Cosman et al., 2017; Bone et al., 2018). In ACTIVE–ACTIVExtend, sequential abaloparatide/alendronate reduced the risk of vertebral, nonvertebral, clinical, and major osteoporotic fractures and increased BMD at the lumbar spine, total hip, and femoral neck compared with sequential placebo/alendronate (Bone et al., 2018).

In this predefined exploratory analysis, we evaluated whether women with postmenopausal osteoporosis, treated with sequential abaloparatide/alendronate or placebo/alendronate across ACTIVE–ACTIVExtend, responded with BMD gains exceeding 3 thresholds: > 0%, representing any positive change, > 3%, and > 6%, representing a more robust increase in bone mass.

2. Materials and methods

2.1. Study participants

Inclusion and exclusion criteria, study design, and methodology of both ACTIVE and ACTIVExtend have been described previously (Miller et al., 2016; Cosman et al., 2017; Bone et al., 2018). Briefly, in ACTIVE, 2463 women with postmenopausal osteoporosis were randomized to receive either blinded daily subcutaneous injections of abaloparatide 80 μg or matching placebo or open-label daily subcutaneous injections of teriparatide 20 μg for 18 months. All patients received supplemental calcium and vitamin D for the study duration and were required to meet a minimal vitamin D level for enrollment in ACTIVE. A total of 606 patients who received abaloparatide in ACTIVE and 637 who received placebo completed the trial, and of these, 1139 patients (92%) were enrolled in ACTIVExtend. Following an off-treatment period of about 1 month for enrollment and to obtain informed consent, patients received weekly alendronate 70 mg monotherapy for 24 months in ACTIVExtend, for a total of 43 months through ACTIVE and ACTIVExtend.

2.2. Responder analysis

The responder analysis was a prespecified exploratory analysis in both ACTIVE and ACTIVExtend, with a responder being defined as a patient with a gain in BMD at all 3 anatomic sites: lumbar spine, total hip, and femoral neck. Three response thresholds were defined: > 0%, > 3%, and > 6%. Applying the same response thresholds, the BMD response was also evaluated for each of the 3 individual sites. Additionally, in a post hoc analysis, we sought to determine how many patients with baseline BMD T-scores ≤ −3.5 at any of the 3 anatomic sites—which represents approximately 25% of patients in each treatment group—experienced improvements in their BMD T-score to > −2.5 and > −2.0 at all 3 anatomic sites.

BMD was measured at the lumbar spine, total hip, and femoral neck at 6, 12, 18, 25, 31, 37, and 43 months during the integrated ACTIVE–ACTIVExtend study period using dual-energy x-ray absorptiometry (DXA) on approved scanners (Hologic, Bedford, MA, USA, or GE Lunar, Madison, WI, USA). For each participant, the same scanner was used at each timepoint to evaluate her BMD. Scanners that were changed during the study were adjusted to correct any differences with the previous scanners (Bioclinica-Synarc, Newark, CA, USA).

2.3. Statistical analyses

This analysis included all 1139 patients in the ACTIVExtend intent-to-treat (ITT) population, comprising those patients who had a baseline BMD and at least 1 post-baseline BMD measurement. No imputation of missing data was performed, and patients who had missing BMD results at any of the 3 anatomic sites at any given timepoint were not included in the "all-anatomic-sites" responder analysis. Analyses at individual anatomic sites included all patients with a baseline and post-baseline assessment at the respective anatomic site and visit.

The chi-square test or Fisher's exact test was used to determine the difference in the proportion of responders between the 2 treatment groups at each visit for each degree of response. BMD changes during alendronate treatment during the ACTIVExtend period were compared using a mixed-effect repeated-measure model. No multiplicity adjustments to the p values were used.

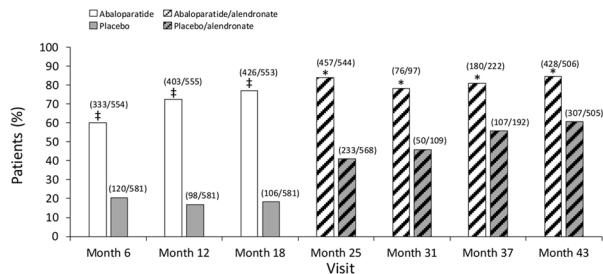## 3. Results

3.1. Disposition and baseline characteristics

Participant disposition and demographic characteristics in ACTIVExtend have been previously published (Bone et al., 2018). Briefly, 558 patients who received abaloparatide and 581 who received placebo in ACTIVE were enrolled in ACTIVExtend. Eighty-eight percent of patients who enrolled in ACTIVExtend completed the study (Bone et al., 2018). There were no clinically meaningful differences in baseline characteristics between ACTIVExtend and full ACTIVE cohorts, and the abaloparatide/alendronate and placebo/alendronate groups were well matched overall. Patients in the placebo/alendronate group had no significant change in mean T-scores between ACTIVE baseline (lumbar spine −2.91, total hip −1.91, and femoral neck −2.17) and ACTIVExtend baseline at 19 months (lumbar spine −2.87, total hip −1.93, and femoral neck −2.20), while patients in the abaloparatide/alendronate group had improvements in BMD T-score from ACTIVE baseline (lumbar spine, −2.88; total hip, −1.88; femoral neck, −2.15) to ACTIVExtend baseline (lumbar spine, −2.11; total hip, −1.63; femoral neck, −1.95). At the start of ACTIVExtend, BMD levels were consistent with prior treatment with abaloparatide and placebo.

3.2. BMD responders at all anatomic sites (lumbar spine, total hip, and femoral neck)
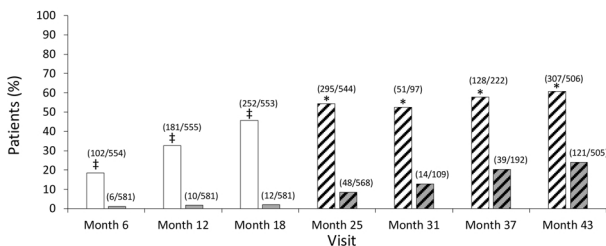
The proportion of patients in each treatment group who were all-site BMD responders at each visit is shown in Fig. 1A–C. At 43 months, a significantly greater percentage of patients in the abaloparatide/alendronate group responded with BMD changes from ACTIVE baseline at all 3 sites and at each of the thresholds of > 0%, > 3%, and > 6% compared with placebo/alendronate (p < 0.001). As the BMD gain threshold increased from > 0% to > 6%, the proportion of responders in the abaloparatide/alendronate group increased relative to that in the placebo/alendronate group.

A significantly greater proportion of patients treated with abaloparatide were also all-site responders at all thresholds at each visit compared with patients treated with placebo. At the threshold of > 3% (Fig. 1B), a significantly greater proportion of responders in the abaloparatide versus placebo group in ACTIVE was maintained through each visit in ACTIVExtend. In ACTIVExtend, at 25 months, 54.2% of patients treated with abaloparatide/alendronate had increases in BMD of > 3% at all 3 anatomic sites compared with 8.5% for placebo/alendronate. Corresponding values at Month 43 were 60.7% of abaloparatide/alendronate patients compared with 24.0% of placebo/alendronate patients. At the > 6% threshold (Fig. 1C), at 25 months, 21.3% of abaloparatide/alendronate patients had BMD responses at all 3 anatomic sites compared with 0.7% of placebo/alendronate patients. At 43 months, 33.2% of abaloparatide/alendronate patients and 4.0% of
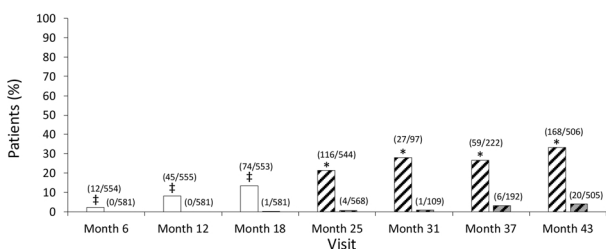
Fig. 1. BMD Responders at All 3 Sites by Visit (ACTIVExtend ITT population).
Note: Fewer patients had BMD measured at Months 31 and 37 (see *Study limitations*).
‡p < 0.001 abaloparatide vs placebo; *p < 0.001 abaloparatide/alendronate vs placebo/alendronate.
Abbreviations: BMD, bone mineral density; ITT, intent-to-treat.

Fig. 2. Proportions of Patients Experiencing Changes in Osteoporosis Status from Baseline BMD T-score ≤ −3.5 to Improved BMD T-score Threshold at All 3 Anatomic Sites at Any Visit Over 43 Months.
Note: Fewer patients had BMD measured at Months 31 and 37 (see *Study limitations*).
*p < 0.05; †p < 0.01; ‡p < 0.001 for abaloparatide vs placebo and for abaloparatide/alendronate vs placebo/alendronate.
Abbreviation: BMD, bone mineral density.

and 4. At 43 months, BMD response rates at the > 3% threshold for the abaloparatide/alendronate group versus the placebo/alendronate group were 93.1% and 79.4% at the lumbar spine, 80.1% and 52.1% at the total hip, and 67.5% and 34.9% at the femoral neck, all p < 0.001. Likewise, at 43 months response rates at the > 6% thresholds were significantly greater in the abaloparatide/alendronate group compared with the placebo/alendronate group for each of the 3 sites (p < 0.001 at each site).

In general, the pattern of change in BMD responses at the individual anatomic sites over the course of the study followed that seen for all-site BMD responses

At each visit there was a significantly greater proportion of patients with > 3% (Fig. 3) or > 6% (Fig. 4) increase in BMD at each site in the abaloparatide/alendronate group compared with the placebo/alendronate group (p < 0.001, all comparisons). The proportion of patients exceeding the 3% and 6% BMD thresholds at each visit at the lumbar spine, total hip, and femoral neck followed a similar pattern to the all-site BMD responses.

A post hoc analysis of change in absolute BMD from ACTIVExtend baseline was conducted (Supplementary Fig. 1). Similar BMD gains were observed during alendronate treatment in ACTIVExtend at the femoral neck regardless of prior treatment with abaloparatide or placebo. Greater BMD gains with alendronate from ACTIVExtend baseline was observed at the lumbar spine (all time points) and total hip (month 24) in the placebo/alendronate arm vs the abaloparatide/alendronate arm. These differences likely reflect the 18 months of no treatment received by patients in the placebo arm of ACTIVE.

An additional post hoc analysis evaluated the proportion of patients who were BMD non-responders as those with BMD loss from ACTIVE baseline of > 3% at any site. Following 18 months of abaloparatide or placebo treatment, 26 of 558 (4.7%) and 214 of 581 (36.8%) in the abaloparatide/alendronate and placebo/alendronate groups, respectively experienced > 3% BMD loss (p < 0.001). At 43 months, 29 of
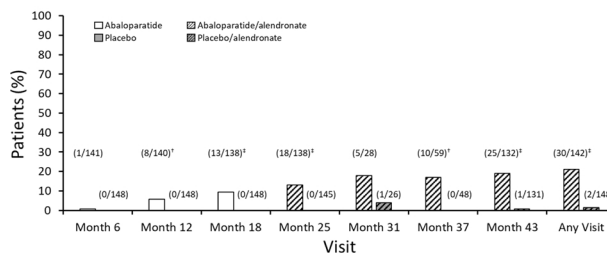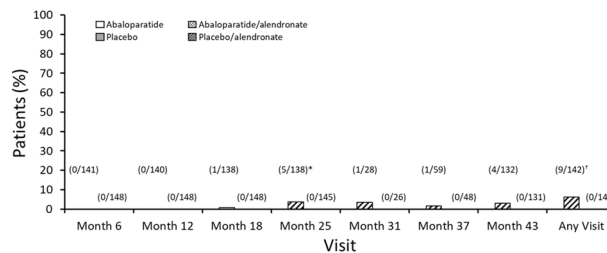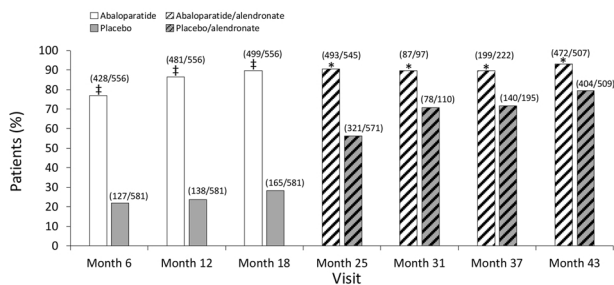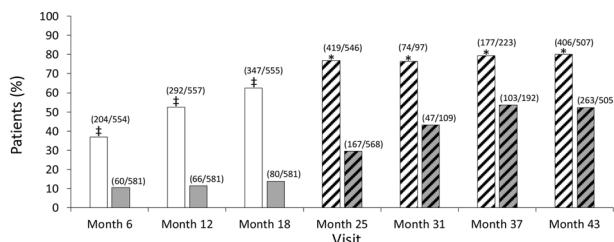
placebo/alendronate patients were responders at the > 6% threshold.

In the abaloparatide/alendronate treatment group, 142 of 558 patients (25.4%) had a baseline BMD T-score ≤ −3.5 at either lumbar spine, total hip, or femoral neck, while in the placebo/alendronate group, 148 of 581 patients (25.5%) had such a score at any site. A post hoc analysis demonstrated that among these subgroups of patients with any baseline BMD T-score ≤ −3.5 (at lumbar spine, total hip, or femoral neck), 30 of 142 (21.1%) abaloparatide/alendronate patients experienced improvement in osteoporosis status such that they achieved BMD T-scores > −2.5 at all 3 anatomic sites at least once at any visit over the full 43 months of the trial (Fig. 2A); among the placebo/alendronate group, 2 of 148 (1.4%) patients experienced such a change in osteoporosis status (p < 0.001 for abaloparatide/alendronate vs placebo/alendronate). Among these patients with any baseline BMD T-score ≤ −3.5, 9 (6.3%) in the abaloparatide/alendronate group versus 0 in the placebo/alendronate group (p < 0.01) achieved a BMD T-score > −2.0 at all 3 anatomic sites at least once at any trial visit (Fig. 2B).

3.3. BMD response rates for individual anatomic sites

BMD responses at the 3 individual anatomic sites at each visit during the 43 months of ACTIVE and ACTIVExtend are shown in Figs. 3

A. Lumbar Spine

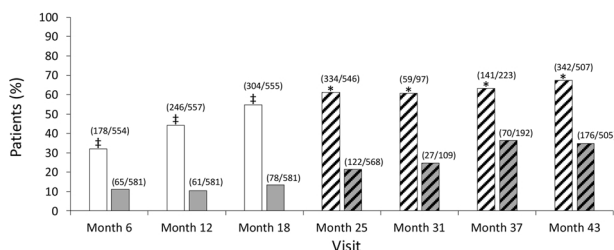

B. Total Hip

C. Femoral Neck

Fig. 3. Proportion of Patients with > 3% BMD Increase from ACTIVE Baseline by Anatomic Site and Visit (ACTIVExtend ITT population).
Note: Fewer patients had BMD measured at Months 31 and 37 (see *Study limitations*).
‡p < 0.001 abaloparatide vs placebo; *p < 0.001 abaloparatide/alendronate vs placebo/alendronate.
Abbreviations: BMD, bone mineral density; ITT, intent-to-treat.

508 (5.7%) and 63 of 509 (12.4%) in the abaloparatide/alendronate and placebo/alendronate groups, respectively experienced > 3% BMD loss (p > 0.001).

4. Discussion

In ACTIVExtend, the fracture risk reduction benefits gained with abaloparatide treatment in ACTIVE were maintained following an additional 24 months of treatment with alendronate (new vertebral fractures: 84% relative risk reduction abaloparatide/alendronate vs placebo/alendronate [p < 0.001]; nonvertebral fractures: 39% risk reduction [p = 0.038]). Consistent with the fracture risk reduction observed in ACTIVE and ACTIVExtend, the current prespecified exploratory responders analysis demonstrated that significantly more patients in the abaloparatide/alendronate group than in the placebo/alendronate group met the definition of a responder at all thresholds of response (< 0%, < 3%, and < 6%) at 43 months by showing increases in BMD from ACTIVE baseline at all 3 anatomic sites (lumbar spine, total hip, and femoral neck). Furthermore, in evaluating patients who

A. Lumbar Spine
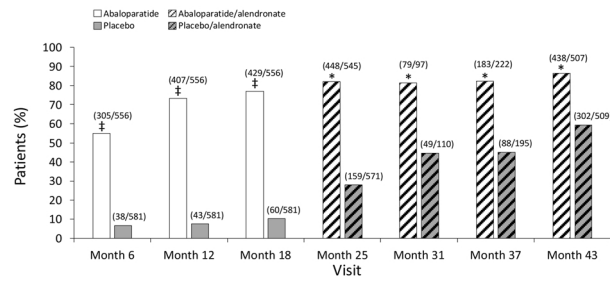
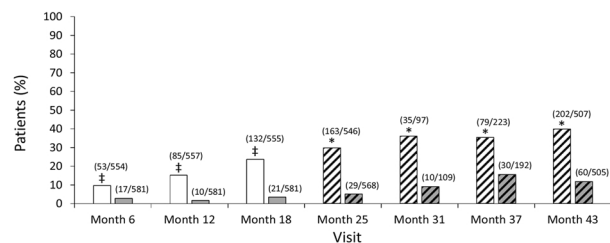**B. Total Hip**
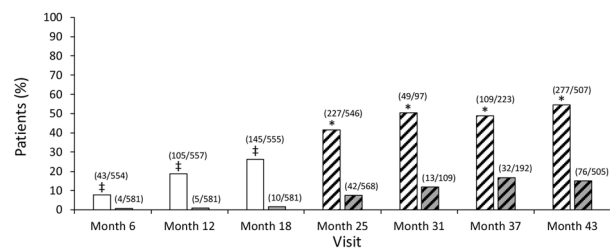
C. Femoral Neck

Fig. 4. Proportion of Patients with > 6% BMD Increase from ACTIVE Baseline by Anatomic Site and Visit (ACTIVExtend ITT population).
Note: Fewer patients had BMD measured at Months 31 and 37 (see *Study limitations*).
‡p < 0.001 abaloparatide vs placebo; *p < 0.001 abaloparatide/alendronate vs placebo/alendronate.
Abbreviations: BMD, bone mineral density; ITT, intent-to-treat.

had BMD T-scores ≤ −3.5 (a level representing those in the lowest BMD quartile of patients enrolled in ACTIVE) at any of the 3 anatomic sites, we found that 21.1% of those treated with abaloparatide followed by alendronate were able to achieve BMD T-scores > −2.5 at all 3 anatomic sites. And finally, a significantly greater proportion of patients in the abaloparatide/alendronate group also had increases at all thresholds at each individual anatomic site than did the placebo/alendronate group at 43 months.

During ACTIVE, the abaloparatide treatment group had a greater proportion of BMD responders at each visit than did the placebo group (Miller et al., 2019). During ACTIVExtend, the proportion of patients with > 3% increase in BMD remained significantly higher in the abaloparatide/alendronate group than in the placebo/alendronate group at each visit. Further, at 43 months, the proportion of patients who met responder thresholds in the abaloparatide/alendronate group was increased, relative to the proportion of responders in the abaloparatide group at the end of ACTIVE. These findings support the foundational effect of anabolic treatment first, followed subsequently by antiresorptive treatment and are consistent with increases in BMD seen in previous studies of antiresorptive treatment following an anabolic agent (Leder et al., 2017; Rittmaster et al., 2000; Black et al., 2005; Leder et al., 2015; Saag et al., 2017).

BMD response rates in the placebo/alendronate group also increased over the duration of ACTIVExtend but to a lower level than those observed in the abaloparatide/alendronate group. These BMD response rates were similar to previous BMD response analyses of patients treated with 24 months of equivalent alendronate dosing (Hochberg et al., 1999; Bonnick et al., 2006). Greater BMD gains with alendronate from ACTIVExtend baseline were observed at the lumbar spine and total hip in the placebo/alendronate arm vs the abaloparatide/alendronate arm, however this likely reflects the 18 months of no treatment received by patients in the placebo arm of ACTIVE.

4.1. Study limitations

This study is limited in that it was exploratory, and subject to the limitations in size and duration of the ACTIVExtend trial. In addition, changes in BMD reported here were calculated relative to ACTIVE baseline in order to include the effects of abaloparatide treatment on BMD in the analysis. Another limitation is a product of study design: A substantially smaller number of patients had BMD measured by DXA at Months 31 and 37 than at Months 25 and 43. A protocol amendment was issued in March 2015 that added DXA assessments at Months 31, 37, and 43. However, by the time the amendment was implemented, many patients had already completed the Months 31 and 37 visits. Therefore, only about 18% of patients had DXA assessments at 31 months, and about 36% had assessments at 37 months.

4.2. Conclusions

A significantly greater proportion of patients were all-site BMD responders to sequential abaloparatide/alendronate compared with placebo/alendronate at all thresholds and at all timepoints, consistent with the significant BMD gains seen with abaloparatide treatment during ACTIVE (Miller et al., 2016) and with the continued fracture risk reduction observed in ACTIVExtend (Bone et al., 2018). These findings provide further evidence that the sequence of an anabolic (abaloparatide) followed by an antiresorptive (alendronate) treatment provides sustained benefit.

Disclosures

Dr. Deal is a speaker for Amgen and Lilly and has participated on scientific advisory boards for Amgen, Eli Lilly, and Radius Health, Inc.; Dr. Mitlak, Dr. Fitzpatrick, and Dr. Wang are employees of, and own stock in Radius Health, Inc.; Dr. Miller is a consultant to Radius Health, Inc., an advisory board member for AgNovos, Alexion, Amgen, Eli Lilly, Merck, Radius Health, Inc., and Roche, and has received research grants from Alexion, Amgen, Boehringer Ingelheim, Immunodiagnostics, Eli Lilly, Merck, Merck Serono, National Bone Health Alliance, Novartis, Novo Nordisk, Roche Diagnostics, and Takeda.

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Radius Health, Inc. developed the statistical analysis plan and analyzed the data. Employees of Radius Health, Inc. contributed as authors of the paper as described above. The final decision to submit the manuscript for publication was made by the authors.

Declaration of Competing Interest

Dr. Mitlak reports personal fees and other from Radius Health, Inc., outside the submitted work.

Dr. Deal reports personal fees from Amgen, personal fees from Eli Lilly and Co, personal fees from Radius Health, Inc., outside the submitted work.

Dr. Fitzpatrick reports personal fees and other from Radius Health, Inc., outside the submitted work.

Dr. Miller reports personal fees from Radius Health, Inc., personal fees from AgNovos, grants and personal fees from Alexion, grants and personal fees from Amgen, grants and personal fees from Eli Lilly and Co, grants and personal fees from Merck & Co, personal fees from Roche, grants from Boerhinger Ingelheim, grants from Immunodiagnostics, grants from Merck Serono, grants from National Bone Health Alliance, grants from Novartis, grants from Novo Nordisk, grants from Roche Diagnostics, grants from Takeda Pharmaceutical Company, outside the submitted work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bonr.2019.100230.

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