Current Medical Research and Opinion

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/icmo20

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**To cite this article:** Paul D. Miller , John P. Bilezikian , Lorraine A. Fitzpatrick , Bruce Mitlak , Eugene V. McCloskey , Felicia Cosman & Henry G. Bone (2020): Abaloparatide: an anabolic treatment to reduce fracture risk in postmenopausal women with osteoporosis, Current Medical Research and Opinion, DOI: 10.1080/03007995.2020.1824897

**To link to this article:** https://doi.org/10.1080/03007995.2020.1824897

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Published online: 12 Oct 2020.

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CURRENT MEDICAL RESEARCH AND OPINION
https://doi.org/10.1080/03007995.2020.1824897
Article RT-0344.R1/1824897

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REVIEW ARTICLE

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# Abaloparatide: an anabolic treatment to reduce fracture risk in postmenopausal women with osteoporosis

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**ABSTRACT**

**Objective:** Fractures due to osteoporosis represent a serious burden on patients and healthcare systems. The objective of this review is to provide an overview of the anabolic agent abaloparatide (ABL) for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

**Methods:** A literature review was conducted using PubMed to identify articles focused on ABL published prior to February 10, 2020, using the search term "abaloparatide".

**Results:** ABL, a synthetic analog of human parathyroid hormone-related protein, increased bone mineral density (BMD), improved bone microarchitecture, and increased bone strength in preclinical and clinical studies. The pivotal phase 3 trial ACTIVE and its extension (ACTIVExtend) demonstrated the efficacy of initial treatment with ABL for 18 months followed by sequential treatment with alendronate (ALN) for an additional 24 months to reduce the risk of vertebral, nonvertebral, clinical, and major osteoporotic fractures and to increase BMD in postmenopausal women with osteoporosis. Discontinuations from ACTIVE were slightly more common in ABL-treated patients due to dizziness, palpitations, nausea, and headache. *Post hoc* analyses of ACTIVE and ACTIVExtend support the efficacy and safety of ABL in relevant subpopulations including postmenopausal women with various baseline risk factors, women ≥80 years, women with type 2 diabetes mellitus, and women with renal impairment.

**Conclusions:** ABL is an effective and well-tolerated treatment for women with postmenopausal osteoporosis at high risk for fracture. Its therapeutic effects are sustained with subsequent ALN therapy.

**ARTICLE HISTORY**
Received 14 May 2020
Revised 31 August 2020
Accepted 15 September 2020

**KEYWORDS**
Abaloparatide; osteoporosis; vertebral fracture; nonvertebral fracture; anabolic

## Introduction

### *Public health burden of osteoporosis and related fractures*

Osteoporosis, a disorder that often occurs with aging, is associated with reduced bone mass, compromised bone strength, and impaired bone quality, resulting in an increased risk of fracture[1,2]. Postmenopausal women are at particular risk for osteoporosis due to estrogen deficiency, with nearly one in two women likely to experience an osteoporosis-related fracture in their lifetime[3]. Over 2 million osteoporotic fractures occur annually in the United States, and this number is projected to grow even larger, to 3 million by 2025[4,5].

Osteoporosis-related fractures are an important public health concern because of related morbidity, mortality, and cost. Excess mortality among patients with hip fractures is ~10–20% in the year following such a fracture[6,7] with as many as two-thirds of patients failing to regain their prior functional status[7,8]. Both clinical vertebral fractures (fractures that come to immediate medical attention) and asymptomatic vertebral fractures (which account for more than two-thirds of all vertebral fractures) are also associated with substantial morbidity and mortality in postmenopausal women[9–11].

Osteoporosis-related fractures are also associated with a significant economic burden. Indeed, hospitalizations for osteoporotic fractures are more frequent than for stroke, heart attack, or breast cancer (Figure 1)[12]. The burden of osteoporotic fractures also includes the unmeasured but very real economic costs due to impairment of such activities as care of grandchildren or volunteer work by "retired" individuals who sustain a fracture, or loss of productivity for caregivers taking care of a fracture patient. Despite this, studies have shown that the vast majority of patients are not treated for osteoporosis following a fracture[13] and rates of

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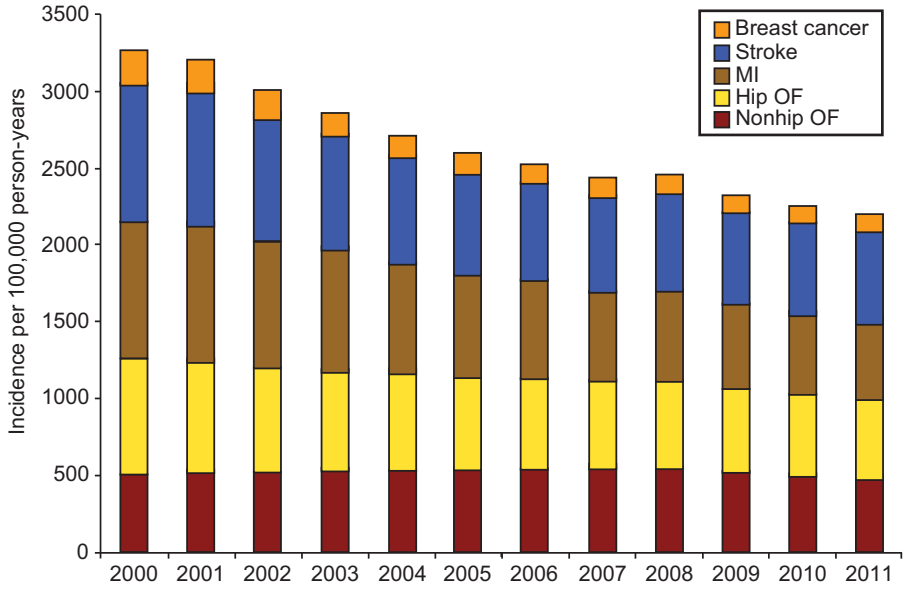



**Figure 1.** Unadjusted rates of hospitalizations for osteoporotic fractures compared with rates for myocardial infarction, stroke, and breast cancer in the United States.[12] MI, myocardial infarction; OF, osteoporotic fracture. Reprinted from *Mayo Clin Proc*, 90(1), Singer A, et al., Burden of illness for osteoporotic fractures compared with other serious diseases among postmenopausal women in the United States, Pages No.53–62, Copyright (2015), with permission from Elsevier.

osteoporosis diagnosis and office-based DXA utilization have declined in recent years[14].

Medications approved for the treatment of osteoporosis in the US include the anabolic agents teriparatide (TPTD), abaloparatide (ABL), and romosozumab, and antiresorptive drugs, including bisphosphonates, denosumab, estrogens, and selective estrogen receptor modulators (SERMs). Anabolic agents stimulate osteoblast production and function resulting in increased bone formation and improved bone microstructure, mass, and strength[15], whereas antiresorptive therapies inhibit osteoclast-mediated bone resorption[16]. Anabolic treatments are recommended for postmenopausal women with osteoporosis at high risk for fracture for a limited duration of treatment[17,18]. Although most guidelines do not define an optimal sequence of treatment, studies suggest the sequence in which anabolics and antiresorptives are used can impact treatment effectiveness[1,19,20]. In general, available data suggest anabolic agents should precede, rather than follow, antiresorptives.

Clearly, timely treatment initiation and the appropriate sequence of treatment are needed for patients at high risk for osteoporotic fractures. The objective of this review is to provide an overview of the anabolic agent ABL for the treatment of postmenopausal women with osteoporosis.

## Methods

A literature review was conducted using PubMed to identify articles focused on ABL published in English prior to February 10, 2020, using the search term "abaloparatide". Articles were excluded if they did not focus primarily on ABL and postmenopausal osteoporosis. Review articles were also excluded.

To ensure inclusion of the most up-to-date research related to ABL, abstracts presenting data from the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE; the pivotal phase 3 trial for ABL) and its extension, ACTIVExtend, at osteoporosis-relevant congresses were also included in this review. Relevant abstracts from the Endocrine Society (ENDO) annual meeting, the American Society for Bone and Mineral Research (ASBMR) annual meeting, the World Congress on Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (WCO), and the American Association of Clinical Endocrinology (AACE) annual meeting from 2016 to 2019, inclusive, are included.

## Results

### *ABL preclinical and early clinical development*

Parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) both signal through the PTH receptor type 1 (PTHR1) with important, but different, effects on bone development and remodeling[21–23]. Studies have demonstrated that PTH and PTHrP bind to different conformations of the PTHR1 receptor with differing affinities[22]. PTH binds with greater affinity than PTHrP[22] to the G-protein uncoupled conformation, $R^0$, which is associated with prolonged cyclic AMP signaling, while PTHrP and PTH bind with similar affinities to the G protein-coupled RG conformation, which results in shorter duration of cyclic AMP response[22]. Therefore, only PTH results in sustained cyclic AMP production, which involves receptor internalization and positive calcium allostery[23–26]. Studies have shown that continuous cyclic AMP signaling favors osteoclast formation and bone resorption while intermittent signaling favors a net anabolic effect[21,27–29]; however, whether this translates to clinically relevant difference with PTH and PTHrP ligands on bone resorption remains to be determined.

ABL is a synthetic analog of human PTHrP (1–34) with 41% sequence homology to PTH (1–34) and 76% sequence homology to PTHrP (1–34) (Figure 2) that binds more

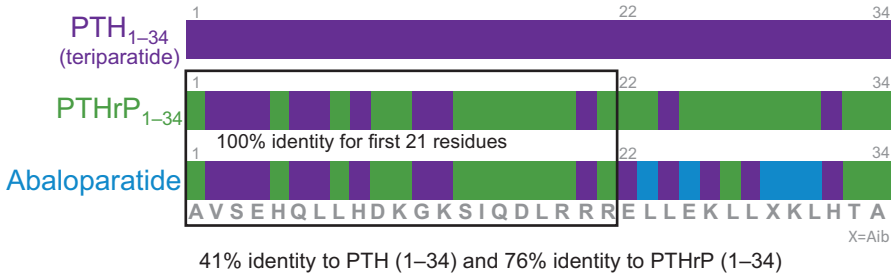



**Figure 2.** Abaloparatide sequence identity with human PTH and PTHrP. Purple represents identity to PTH (1–34). Green represents identity to PTHrP (1–34). Blue represents substitute residues in abaloparatide. Abbreviations. PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein.

selectively to the RG versus the $R^0$ PTHR1 conformation[30,31]. ABL binds to the $R^0$ confirmation with an ~80-fold weaker affinity than that observed for TPTD and the affinities for the RG versus $R^0$ conformation differed by 1600-fold for ABL versus 12-fold for TPTD.

In preclinical studies, ABL increased bone mass and bone formation and improved bone microarchitecture. These results were correlated with increased bone strength in ovariectomized (OVX) rats and cynomolgus monkeys[30,32–35]. Specifically, 12 months of ABL treatment in OVX rats led to dose-dependent improvements in bone mass, geometry, and strength with evidence of bone quality preservation or improvement[30,34]. Studies in cultured cells and animal models have shown that the effects of ABL on bone may occur with greater increase in markers of bone formation and less resorptive activity, including reduced stimulation of factors involved in bone resorption, compared with TPTD[35–39]. Less resorptive activity was observed with ABL versus TPTD at the same equimolar concentrations and at a 1:4 higher ration of ABL to TPTD[39]. Another recent study directly compared the *in vivo* and *in vitro* effects of TPTD and ABL, providing new evidence that ABL exhibits greater osteoanabolic response and higher cAMP stimulation and β-arrestin recruitment than TPTD[38]. Taken together, these findings would suggest that differences in cAMP stimulation by TPTD versus ABL could be responsible for the distinct anabolic actions on bone.

In OVX cynomolgus monkeys, 16 months of ABL treatment increased bone formation, bone density, and bone strength with no apparent effects on bone resorption or serum calcium[33]. Bone quality was preserved at purely cortical sites and was maintained or improved at trabecular-rich sites; however, ABL did not increase cortical porosity. In a separate study, TPTD was shown to increase bone resorption and cortical porosity in a dose-dependent manner in OVX cynomolgus monkeys, however, the effects on cortical porosity did not adversely affect bone strength[40,41]. PTH (1–84) has also been shown to increase cortical porosity in OVX cynomolgus monkeys, but only at the highest of three doses studied (25 μg per kg), which is estimated to result in 13-fold higher exposure than the dose used in humans[42,43].

As with all PTHR1 agonists, a dose-dependent increase in the incidence of osteosarcoma has been observed in rats treated chronically for up to 2 years with ABL at doses estimated to result in 3-, 11-, and 22-fold greater exposure than the 80 μg/day dose approved for short-term use in humans[44]. The incidence of neoplastic changes in long-term rodent toxicology studies was similar between ABL and TPTD. Increased risk of osteosarcoma was not observed with TPTD in cynomolgus monkeys[45]. Postmarketing surveillance has not observed an association between TPTD treatment and osteosarcoma in humans after more than 17 years of clinical use[46,47]; no cases of osteosarcoma have been reported in humans treated with ABL at approximately 2 years post-launch (Radius Health, Inc.).

Early clinical trials in postmenopausal women with osteoporosis showed beneficial effects of ABL on BMD and trabecular bone score (TBS), an indirect measure of bone microarchitecture[48,49]. In a 24-week, phase 2 dose-finding study, 222 women with postmenopausal osteoporosis were randomly assigned to receive daily subcutaneous injections of placebo (PBO); ABL 20, 40, and 80 μg; or TPTD 20 μg[48]. BMD increased in a dose-dependent manner with ABL treatment, and increases in BMD were greater with ABL versus PBO at the lumbar spine (40 μg and 80 μg, $p < .001$), femoral neck (80 μg, $p = .036$), and total hip (80 μg, $p = .007$). Increases in total hip BMD were greater in the ABL 40 μg ($p = .047$) and 80 μg ($p = .006$) groups compared with the group receiving TPTD. ABL also increased TBS versus PBO in the 20, 40, and 80 μg groups ($p < .001$ for all groups at 24 weeks)[49]. Increase in TBS was also significantly greater with 80 μg ABL versus TPTD ($p = .04$).

The proportion of participants who experienced treatment-emergent adverse events (TEAEs) was similar across all treatment groups. Most TEAEs were mild to moderate in severity[48]. Overall, arthralgia and urinary tract infection (15% each); bronchitis, influenza, and nasopharyngitis (9% each); and anemia, back pain, dizziness, dyslipidemia, hypercalciuria, and injection site hematoma (7% each) were the most common adverse events (AEs).

## ABL pivotal trials: ACTIVE and ACTIVExtend

ACTIVE was the pivotal multicenter, multinational, double-blind, PBO- and active-controlled, phase 3 fracture-prevention trial for ABL in postmenopausal women with osteoporosis[50]. Osteoporosis was defined by BMD and/or fracture criteria. A total of 2463 women aged 49–86 years with osteoporosis were randomized 1:1:1 to receive daily subcutaneous injections of PBO, ABL 80 μg, or open-label active comparator TPTD 20 μg for 18 months (Figure 3). 1901 women completed the study (73.5% [$n = 606$] in the ABL group, 77.6% [$n = 637$] in the placebo group, and 80.4% [$n = 658$] in the

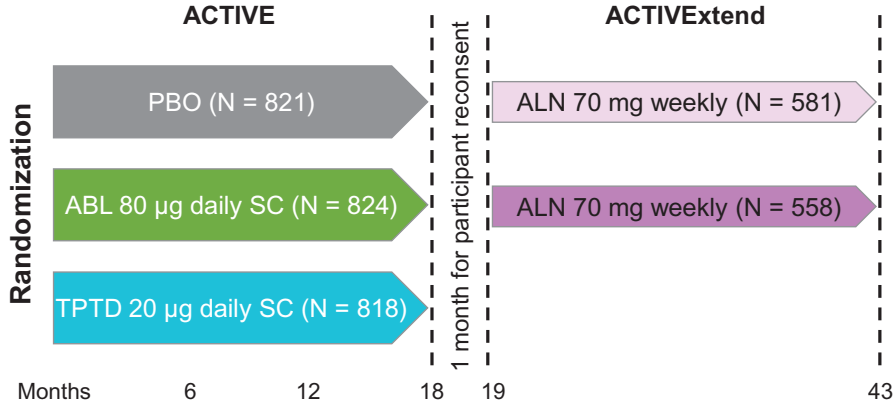



**Figure 3.** ACTIVE and ACTIVExtend study design[51]. Abbreviations. ABL, abaloparatide; ALN, alendronate; PBO, placebo; SC, subcutaneous; TPTD, teriparatide. Adapted from Bone et al., *J Clin Endocrinol Metab*, August 2018, 103(8):2949–2957. Copyright 2018 CC BY License.

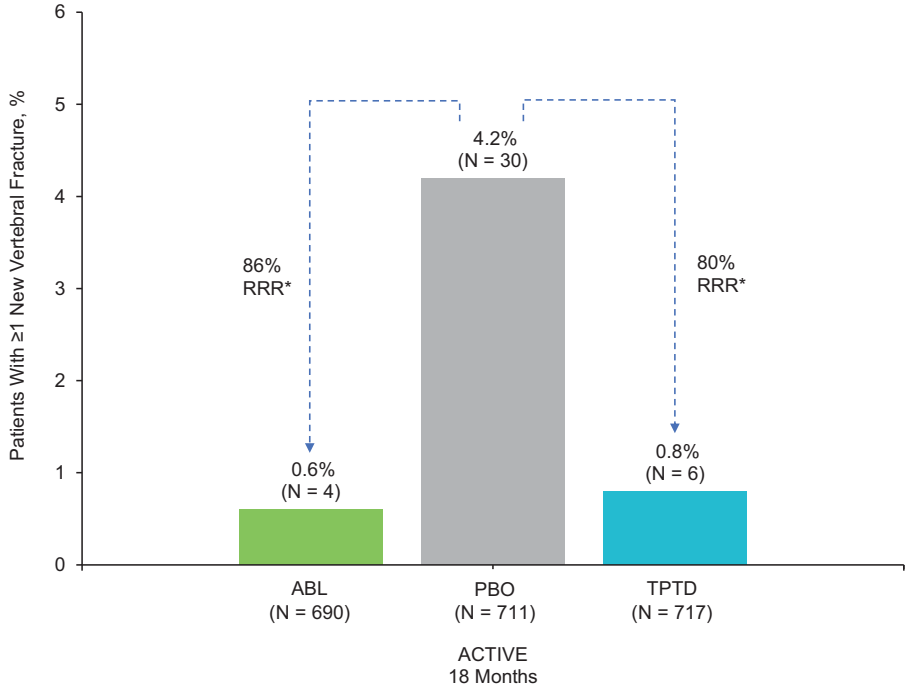



**Figure 4.** Incidence of new vertebral fractures in ACTIVE (months 0–18)[50]. New vertebral fractures occurred in 0.6% of patients in the ABL group versus 4.2% in the PBO group (RD versus PBO, −3.64 [95% CI, −5.42 to −2.10]; relative risk, 0.14 [95% CI, 0.05 to 0.39]; $p < .001$. New vertebral fractures occurred in 0.8% of patients in the TPTD group (RD versus PBO, −3.38 [95% CI, −5.18 to −1.80]; relative risk, 0.20 [95% CI, 0.08 to 0.47]; $p < .001$). New vertebral fractures included clinical and nonclinical fractures assessed by radiograph. *$p < .001$; ABL, abaloparatide; CI, confidence interval; PBO, placebo; RD, risk difference; RRR, relative risk reduction; TPTD, teriparatide.

TPTD group). At the end of ACTIVE, participants who received ABL or PBO were offered enrollment in the ACTIVExtend extension study[51,52]. There were 1139 women (92% of those eligible) enrolled in ACTIVExtend and treated with ALN 70 mg weekly for 24 months. A 1-month rollover period from the end of ACTIVE to enrollment in ACTIVExtend was allowed.

## *ACTIVE*

Groups were well matched at baseline with an overall mean age of 68.8 years, mean spine and total hip BMD T-score of −2.9 and −1.9, respectively, prior vertebral fracture in 24% of participants, and a history of nonvertebral fracture within the past 5 years in 31% of participants[50]. Daily subcutaneous administration of ABL 80 µg for 18 months significantly reduced the risk of new vertebral fractures by 86% versus PBO, with new vertebral fractures occurring in only 0.6% of participants in the ABL group versus 4.2% in the PBO group ($p < .001$) (Figure 4)[50]. TPTD also reduced the risk of new vertebral fractures by 80% versus PBO ($p < .001$).

In addition, nonvertebral time-to-event curves suggest early fracture risk reduction with ABL (Figure 5). ABL significantly reduced the risk of nonvertebral (by 43%), clinical (by 43%), and major osteoporotic (by 70%) fractures versus PBO. In contrast, Kaplan-Meier estimated event rates for nonvertebral, clinical, and major osteoporotic fractures were not significantly different with TPTD compared with PBO. Although this study was not powered for a comparison between ABL and TPTD, a reduction in the risk of major osteoporotic

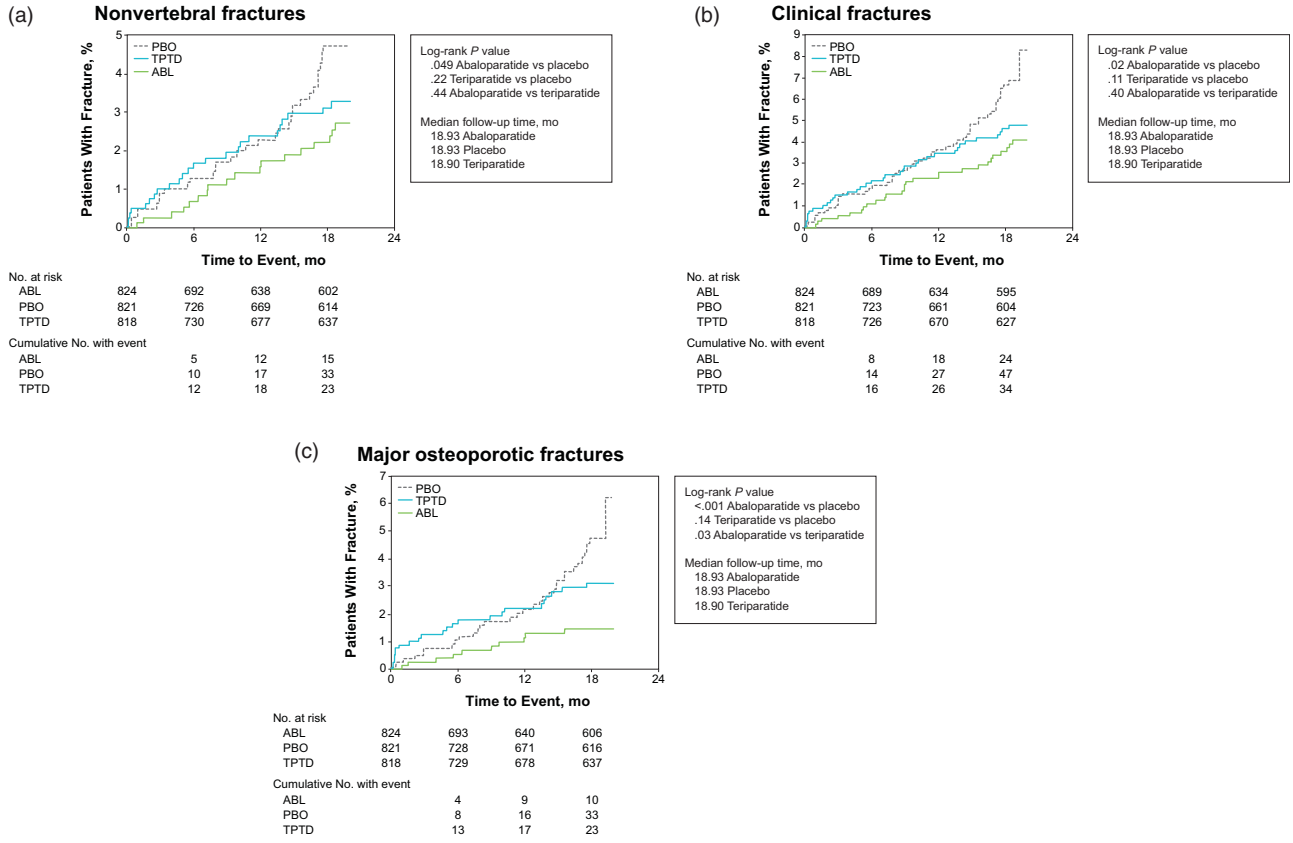



**Figure 5.** Time to event of (a) nonvertebral, (b) clinical, and (c) major osteoporotic fractures in ACTIVE[50]. (a) Kaplan–Meier curves indicate time to the first nonvertebral fracture—a prespecified secondary end point. Nonvertebral fractures were defined as fractures excluding those of the spine, sternum, patella, toes, fingers, skull, and face and those with high trauma. For abaloparatide versus placebo, the HR was 0.57 (95% CI, 0.32–1.00; $p = .049$) and for teriparatide versus placebo, the HR was 0.72 (95% CI, 0.42–1.22; $p = .22$). (b) Curves indicate time to the first clinical fracture—a prespecified exploratory end point. Clinical fractures were defined as all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine. For abaloparatide versus placebo, the HR was 0.57 (95% CI, 0.35–0.91; $p = .02$) and for teriparatide versus placebo, the HR was 0.71 (95% CI, 0.46–1.09; $p = .11$). (c) Curves indicate time to the first major osteoporotic fracture—a prespecified exploratory end point. Major osteoporotic fractures were defined as fractures of the wrist, upper arm, hip, and clinical spine. For abaloparatide versus placebo, the HR was 0.30 (95% CI, 0.15–0.61; $p < .001$) and for teriparatide versus placebo, the HR was 0.67 (95% CI, 0.39–1.14; $p = .14$). The median durations in days of follow-up for all three fracture categories were 568 (IQR, 557–572) for placebo, 568 (IQR, 477–572) for abaloparatide, and 567 (IQR, 558–571) for TPTD. Abbreviations. ABL, abaloparatide; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; PBO, placebo; TPTD, teriparatide. Reproduced with permission from *Journal of the American Medical Association* 2016. 316(7): 722–733. Copyright © (2016) American Medical Association. All rights reserved.

fractures was observed with ABL versus TPTD, with major osteoporotic fractures occurring in 1.5% of the ABL group versus 3.1% of the TPTD group.

ABL treatment was associated with significantly increased BMD versus PBO; BMD changes at 18 months for ABL versus PBO were 4.2 versus −0.1% at the total hip (treatment difference, 4.3% [95% CI, 3.9–4.6%; $p < .001$]), 3.6 versus −0.4% at the femoral neck (treatment difference, 4.0% [95% CI, 3.6–4.5%; $p < .001$]), and 11.2 versus 0.6% at the lumbar spine (treatment difference, 10.4% [95% CI, 9.8–11.0%; $p < .001$]). Significant increases in total hip, femoral neck, and lumbar spine BMD were also seen at 6 months and 12 months with ABL versus PBO. Improvements in BMD at the total hip and femoral neck were significantly greater with ABL than with TPTD at all time points, and at the lumbar spine significantly greater at 6 and 12 months, but not at 18 months.

Changes in bone turnover markers with ABL treatment were consistent with changes in BMD with ABL[50,53]. An early increase (at 1 month) in the bone formation marker serum procollagen type 1 N-terminal propeptide (s-PINP) was seen with both ABL and TPTD. After 3 months, s-PINP levels trended higher with TPTD than with ABL, though levels remained above baseline throughout 18 months in both groups. Concurrently, serum C-terminal telopeptide of type 1 collagen (s-CTX), a bone resorption marker, increased to a lesser extent with ABL versus TPTD at all time points, supporting the hypothesis that ABL might be associated with less bone resorption compared with TPTD. A *post hoc* analysis to examine the relationship between early markers of bone turnover and BMD found that changes in s-PINP 3 months posttreatment were correlated with subsequent changes in lumbar spine BMD at 18 months in both ABL-treated and TPTD-treated participants in the ACTIVE trial[53]. Absolute levels of s-PINP and s-CTX were lower with ABL compared to TPTD; however, the balance between markers of bone formation and resorption was similar, indicating that BMD increases with ABL with less bone resorption. The balance of bone formation and resorption with ABL resulted in earlier and greater increases in BMD at the spine and total hip, which remained greater at the hip over 18 months.

No differences were seen in serious AEs between treatment groups; however, more AEs leading to study discontinuation occurred in the ABL group (9.9%) than in the TPTD (6.8%) or PBO (6.1%) groups. AEs leading to discontinuation

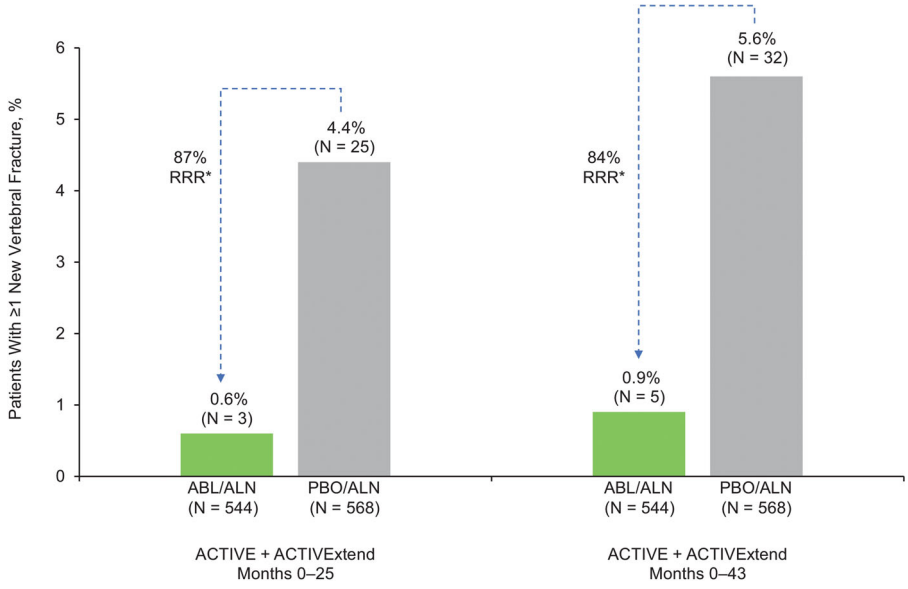



**Figure 6.** Incidence of new vertebral fractures in ACTIVE/ACTIVExtend (months 0–25 and months 0–43)[51,52]. New vertebral fractures occurred in 0.6% of patients in the ABL/ALN group versus 4.4% in the PBO/ALN group at month 25 (relative risk, 0.13; $p < .001$) and 0.9% of patients in the ABL/ALN group versus 5.6% in the PBO/ALN group at month 43 (relative risk, 0.16; $p < .001$). *$p < .001$; Abbreviations. ABL/ALN, abaloparatide followed by alendronate; PBO/ALN, placebo followed by alendronate; RRR, relative risk reduction. Adapted from Bone et al, *J Clin Endocrinol Metab*, August 2018, 103(8):2949–2957, under the CC BY License. Adapted from Mayo Clin Proc., 92/2, Cosman F, et al. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial. p. 200–210, Copyright (2017) with permission from Elsevier.

were generally mild to moderate in severity and included nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%), symptoms associated with vasodilation. Orthostatic hypotension (a decrease in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg from a supine position to standing in a postdose measurement), an AE of special interest in the study, occurred at a similar incidence across groups (ABL 17.1%, PBO 16.4%, TPTD 15.5%). Hypercalcemia was a prespecified study endpoint based on serum calcium concentrations obtained both pre-injection and 4 h post-injection on day 1, and months 1, 3, 6, 9, and 12; and pre-injection only at month 18. Its incidence was lower with ABL (3.4%) versus TPTD (6.4%) (risk difference, −2.96% [95% CI, −5.12 to −0.87]; $p = .006$), consistent with less bone resorption with ABL. There was no evidence of increased cardiovascular risk associated with hypercalcemia in the ABL or TPTD groups. Finally, transiliac crest bone biopsies obtained between months 12 and 18 in ACTIVE showed no adverse effects on bone quality in participants treated with ABL or TPTD[54].

## *ACTIVExtend*

ACTIVExtend included patients from the two arms initially treated with PBO or ABL, but not the open-label TPTD arm of ACTIVE. The reductions in fracture risk achieved with 18 months of ABL treatment in ACTIVE were sustained with subsequent open-label ALN 70 mg given orally once per week for an additional 24 months (cumulative 43 months)[51]. Notably, during the extension wherein all subjects received open-label ALN, the relative risk reduction for vertebral fractures in the original active ABL group, versus those who had received PBO, demonstrated a persistent advantage. After 6 months of ALN monotherapy (between months 19–25), no new vertebral fractures were reported in the group who received ABL followed by ALN (ABL/ALN) compared with 7 in the group who received PBO followed by ALN (PBO/ALN). At cumulative month 25, there was an 87% relative risk reduction in the incidence of new vertebral fractures in the ABL/ALN group versus the PBO/ALN group ($p < .001$) and, at cumulative month 43, an 84% relative risk reduction ($p < .001$)[52] (Figure 6). Participants in the ABL/ALN group versus those in the PBO/ALN group also demonstrated significant reductions in the incidence of nonvertebral fractures, clinical fractures, and major osteoporotic fractures at cumulative month 25 and cumulative month 43 (Figure 7). Although the study was not originally designed to assess hip fracture risk, a supplemental analysis in the ACTIVE intent-to-treat (ITT) plus ACTIVExtend ITT populations was done for regulatory authorities. No hip fractures were reported in the ABL/ALN group versus 5 in the PBO/ALN group.

Gains in BMD at the lumbar spine, total hip, and femoral neck that occurred with ABL treatment versus PBO in ACTIVE were sustained and further enhanced during 24 months of monotherapy with ALN in ACTIVExtend.

The overall incidence of AEs, including severe and serious AEs, was similar between groups while all participants received the same treatment (ALN). The most commonly reported AEs were arthralgia, upper respiratory tract infection, and back pain.

## *ACTIVE and ACTIVExtend* post hoc *analyses*

A number of *post hoc* analyses of ACTIVE and ACTIVExtend have been conducted to further elucidate the efficacy of ABL in postmenopausal women with osteoporosis[53,55–68].

These include further exploration of the BMD effects of ABL in ACTIVE and ACTIVExtend. A prespecified responder analysis[58,68] found that a significantly greater proportion of

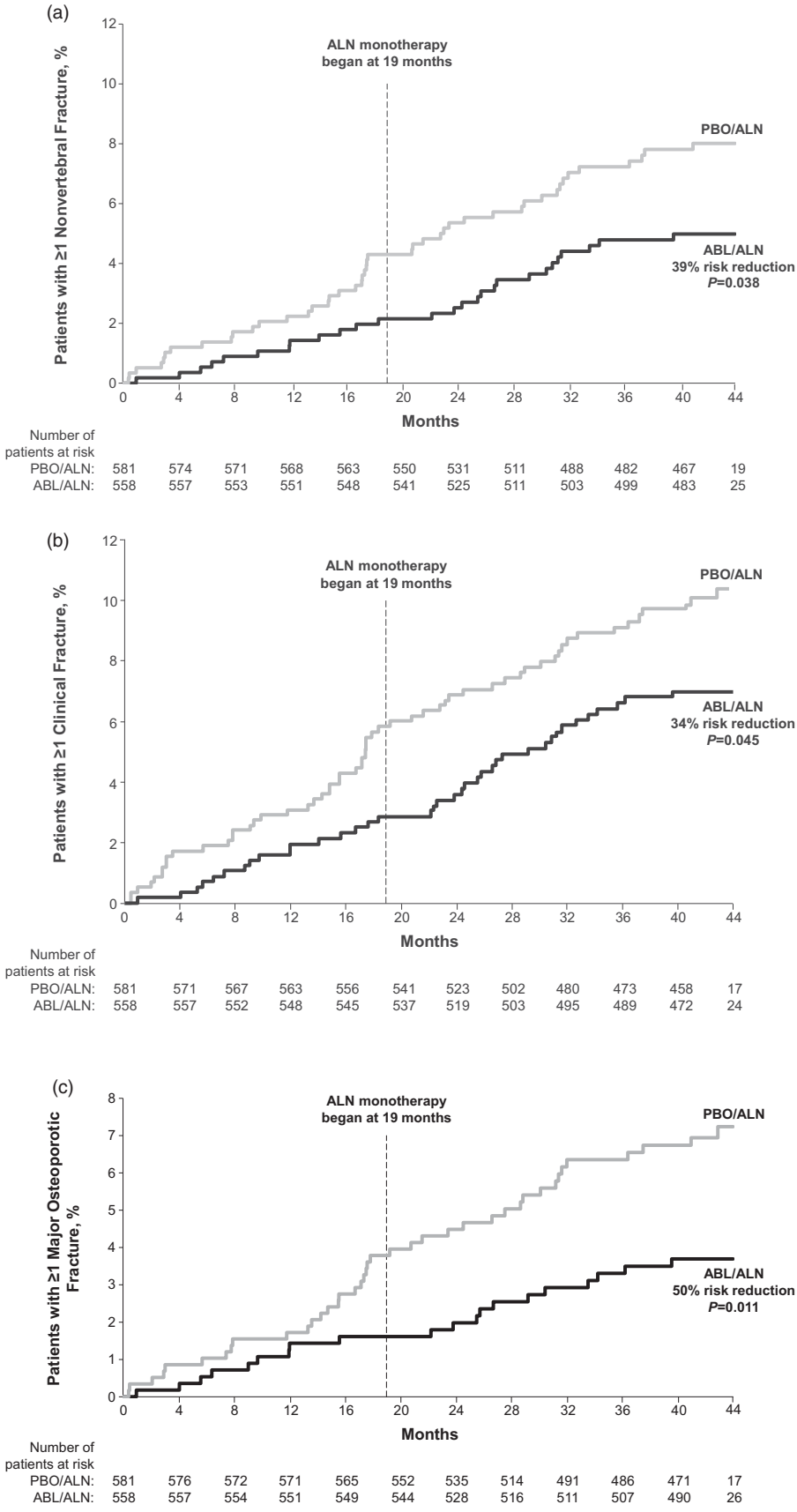



**Figure 7.** Time to event of (a) nonvertebral, (b) clinical, and (c) major osteoporotic fractures in ACTIVE/ACTIVExtend (months 0–43)[51]. Kaplan–Meier curves of time to the first (a) nonvertebral, (b) clinical, and (c) major osteoporotic fracture. Abbreviations. ABL/ALN, abaloparatide followed by alendronate; PBO/ALN, placebo followed by alendronate. Reproduced from Bone et al, *J Clin Endocrinol Metab*, August 2018, 103(8):2949–2957, under the CC BY License.

**Table 1.** Efficacy and safety of ABL in various subpopulations from ACTIVE and ACTIVExtend.

| The efficacy and safety of ABL are consistent with the overall ACTIVE/ACTIVExtend population in the following subpopulations |
|---|
| Patient baseline fracture risk[64,66] |
| • BMD T-score of the lumbar spine, total hip, and femoral neck ($\leq$−2.5 versus >−2.5 and $\leq$−3.0 versus >−3.0) |
| • History of nonvertebral fracture (yes versus no) |
| • Prevalent vertebral fracture (yes versus no) |
| • Age (<65 versus 65 to <75 versus $\geq$75 years) |
| Fracture risk as assessed by FRAX[62] |
| Fracture risk based on CHMP thresholds[60] |
| • Baseline 10-year risk of major osteoporotic fracture $\geq$10% or hip fracture $\geq$5% |
| The elderly[55,63] |
| • Aged $\geq$80 years |
| Patients with renal impairment[57] |
| • Baseline eGFR of $\geq$90 mL/min (stage I CKD) |
| • Baseline eGFR 60 mL/min to <90 mL/min (stage II CKD) |
| • Baseline eGFR 30 mL/min to <60 mL/min (stage III CKD) |
| Patients with T2DM[59] |
| Across geographic and ethnic subgroups[67] |
| • North America, South America, Europe, and Asia |
| • Hispanic, Latino, or other |

Abbreviations. BMD, bone mineral density; CHMP, Committee for Medicinal Products for Human Use; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FRAX, fracture risk assessment tool; T2DM, type 2 diabetes mellitus.

participants treated with ABL compared with both PBO and TPTD had BMD gains at all three anatomic sites (total hip, lumbar spine, and femoral neck) at each threshold (>0, >3.0, and >6.0%) in ACTIVE[58]. This trend continued in ACTIVExtend with significantly more participants in the ABL/ALN group experiencing increases of >0, >3.0, and >6.0% at each anatomical site compared with the PBO/ALN group at 43 months ($p < .001$)[68]. In addition, the effect of ABL on wrist BMD, including anatomical sites with a high proportion of trabecular bone (the ultra distal radius) and cortical bone (1/3 radius) was examined[56,65]. ABL significantly increased BMD at the ultra distal radius versus PBO and TPTD at 18 months in ACTIVE[56]. BMD at the 1/3 distal radius was not significantly different with ABL versus PBO but declined with TPTD versus ABL and PBO. The BMD gains at the ultra distal radius following treatment with ABL in ACTIVE were maintained over the subsequent 24 months of treatment with ALN in ACTIVExtend[65]. Although not significantly different due to low numbers of events, the incidence of wrist fracture in ACTIVE and ACTIVExtend was numerically lower with ABL/ALN versus PBO/ALN.

*Post hoc* analyses of ACTIVE have also examined the efficacy of ABL in various subpopulations including based on patient baseline risk, age, in patients with renal impairment, in patients with type 2 diabetes, and across geographic and ethnic subgroups (Table 1). The fracture risk reduction and BMD increases observed in ACTIVE and ACTIVExtend were found to be consistent regardless of participant baseline fracture risk[64,66] (Figure 8). Fracture risk reduction was also similar across a wide range of baseline fracture probabilities, as assessed by FRAX in women from ACTIVE[62], including in participants at high risk of fracture ($N = 1400$) based on the Committee for Medicinal Products for Human Use (CHMP) guidelines for clinical trial enrollment (a baseline 10-year risk of major osteoporotic fracture $\geq$10% or hip fracture $\geq$5%)[60]. Fracture risk reduction with ABL was also consistent in participants from ACTIVE across geographic region subgroups (North America, South America, Europe, and Asia) and regardless of ethnicity subgroup (Hispanic or Latino or other)[67].

In women aged $\geq$80 years ($n = 94$), ABL significantly increased BMD at the total hip, femoral neck, and lumbar spine to a similar extent as in the overall ACTIVE population[63]. These effects were sustained with ALN treatment in ACTIVExtend[55]. The overall number of fractures in both ACTIVE and ACTIVExtend was too low in this elderly population to draw any conclusions. The safety profiles were similar for the ACTIVE and ACTIVExtend overall populations and the $\geq$80 years subgroup. Importantly, in a *post hoc* analysis of ACTIVE that examined the impact of renal impairment on the efficacy and safety of ABL, there were no detectable differences in BMD changes, fracture risk reduction, and AEs in participants with different degrees of baseline renal function (eGRF <60, 60 to <90, and $\geq$90 mL/min)[57].

Finally, in the subgroup of postmenopausal women with T2DM in ACTIVE ($n = 198$), ABL treatment resulted in significant improvements in BMD at total hip, femoral neck, and lumbar spine compared with PBO, consistent with the overall ACTIVE population[59]. Significant ($p < .001$) improvements in TBS at the lumbar spine (3.72 versus −0.56%) were observed with ABL versus PBO at 18 months, suggesting improvements in bone microarchitecture, which may be impaired in individuals with T2DM. Results were similar for TPTD versus PBO. Fracture event numbers were low due to the small size of this subpopulation and not significantly different between groups.

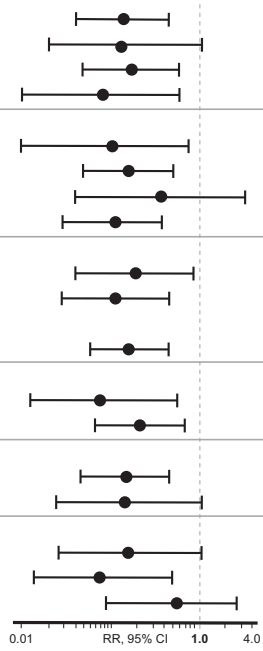
### ABL compared with other osteoporosis treatments

Current evidence suggests that anabolic agents induce a more rapid and greater reduction in both vertebral and nonvertebral fractures than seen with antiresorptive agents. However, head-to-head blinded comparisons of ABL versus other osteoporosis therapies are not available. Summarized above is the only ABL study that utilized TPTD as an active comparator (treatment assignments were randomized but open-label).

In addition, the efficacy of ABL compared with ALN has been indirectly examined in a *post hoc* analysis of ACTIVE

(a)

| | PBO n/N | ABL-SC n/N | RR (95% CI) | Interaction *P* value[a] |
|---|---|---|---|---|
| **Lumbar spine BMD T-score** | | | | |
| ≤−2.5 | 23/543 | 3/507 | **0.14** (0.04, 0.46) | 0.960 |
| >−2.5 | 7/168 | 1/183 | **0.13** (0.02, 1.05) | |
| ≤−3.0 | 17/370 | 3/361 | **0.18** (0.05, 0.61) | 0.493 |
| >−3.0 | 13/341 | 1/329 | **0.08** (0.01, 0.61) | |
| **Total hip BMD T-score** | | | | |
| ≤−2.5 | 11/174 | 1/155 | **0.10** (0.01, 0.78) | 0.699 |
| >−2.5 | 19/537 | 3/535 | **0.16** (0.05, 0.53) | |
| ≤−3.0 | 3/55 | 1/50 | **0.37** (0.04, 3.41) | 0.356 |
| >−3.0 | 27/656 | 3/640 | **0.11** (0.03, 0.37) | |
| **Femoral neck BMD T-score** | | | | |
| ≤−2.5 | 11/210 | 2/198 | **0.19** (0.04, 0.86) | 0.588 |
| >−2.5 | 19/501 | 2/492 | **0.11** (0.03, 0.46) | |
| ≤−3.0 | 5/71 | 0/60 | NA | 0.403 |
| >−3.0 | 25/640 | 4/630 | **0.16** (0.06, 0.46) | |
| **Prevalent vertebral fracture** | | | | 0.371 |
| Yes | 15/165 | 1/147 | **0.07** (0.01, 0.56) | |
| No | 15/546 | 3/543 | **0.20** (0.06, 0.69) | |
| **Prior nonvertebral fracture** | | | | 0.984 |
| Yes | 22/349 | 3/343 | **0.14** (0.04, 0.46) | |
| No | 8/362 | 1/347 | **0.13** (0.02, 1.04) | |
| **Age, years** | | | | 0.209 |
| <65 | 8/131 | 1/126 | **0.13** (0.02, 1.02) | |
| 65 to <75 | 18/459 | 1/437 | **0.06** (0.01, 0.44) | |
| ≥75 | 4/121 | 2/127 | **0.48** (0.09, 2.55) | |




(b)

| | PBO n/N | ABL-SC n/N | HR (95% CI)[b] | Interaction *P* value[c] |
|---|---|---|---|---|
| **Lumbar spine BMD T-score** | | | | |
| ≤−2.5 | 26/631 | 14/603 | **0.58** (0.30, 1.12) | 0.879 |
| >−2.5 | 7/190 | 4/220 | **0.53** (0.16, 1.82) | |
| ≤−3.0 | 21/431 | 7/440 | **0.34** (0.14, 0.79) | 0.082 |
| >−3.0 | 12/390 | 11/383 | **0.98** (0.43, 2.21) | |
| **Total hip BMD T-score** | | | | |
| ≤−2.5 | 12/199 | 6/185 | **0.56** (0.21, 1.49) | 0.951 |
| >−2.5 | 21/621 | 12/637 | **0.58** (0.28, 1.18) | |
| ≤−3.0 | 2/65 | 1/56 | **0.58** (0.05, 6.42) | 0.968 |
| >−3.0 | 31/755 | 17/766 | **0.56** (0.31, 1.02) | |
| **Femoral neck BMD T-score** | | | | |
| ≤−2.5 | 11/242 | 5/240 | **0.48** (0.17, 1.38) | 0.707 |
| >−2.5 | 22/578 | 13/582 | **0.61** (0.31, 1.21) | |
| ≤−3.0 | 4/81 | 3/76 | **0.86** (0.19, 3.83) | 0.567 |
| >−3.0 | 29/739 | 15/746 | **0.53** (0.29, 0.99) | |
| **Prevalent vertebral fracture** | | | | 0.622 |
| Yes | 10/188 | 4/177 | **0.44** (0.14, 1.41) | |
| No | 23/632 | 14/647 | **0.62** (0.32, 1.20) | |
| **Prior nonvertebral fracture** | | | | 0.790 |
| Yes | 19/416 | 11/405 | **0.60** (0.29, 1.27) | |
| No | 14/405 | 7/419 | **0.52** (0.21, 1.28) | |
| **Age, years** | | | | 0.230 |
| <65 | 9/161 | 3/152 | **0.35** (0.09, 1.29) | |
| 65 to <75 | 14/512 | 12/517 | **0.90** (0.42, 1.96) | |
| ≥75 | 10/148 | 3/155 | **0.29** (0.08, 1.07) | |

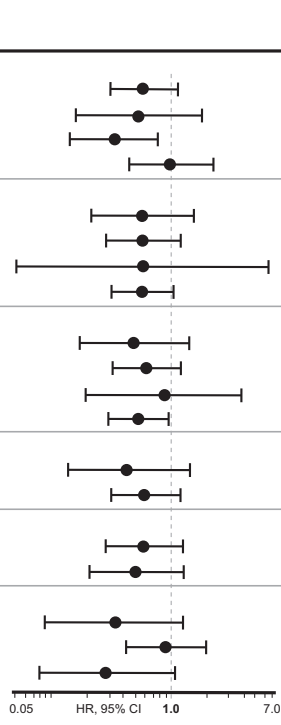



**Figure 8.** Relative risk ratio of new vertebral fractures (a) and hazard ratio of nonvertebral fractures (b) with abaloparatide versus placebo by prespecified subgroup in ACTIVE[64]. [a]Based on the Breslow-Day test for homogeneity of odds ratios between ABL-SC and placebo groups across the subgroup categories. [b]Hazard ratios were calculated within each subgroup category. [c]Based on the Cox proportional hazard model that includes main effects of treatment and subgroup and treatment-by-subgroup interaction. Lowercase n refers to the number of participants in each category with a new vertebral (a) or nonvertebral fracture (b). Uppercase N's refer to the population size for each category. Abbreviations. ABL, abaloparatide; BMD, bone mineral density; CI, confidence interval; HR, hazard ratio; PBO, placebo; RR, relative risk; SC, subcutaneous. Reprinted with permission from Cosman et al. Effects of Abaloparatide-SC on Fractures and Bone Mineral Density in Subgroups of Postmenopausal Women With Osteoporosis and Varying Baseline Risk Factors *J Bone Miner Res.* 2017;32(1):17–23. doi:10.1002/jbmr.2991. Copyright 2016 American Society for Bone and Mineral Research, John Wiley & Sons Inc. All rights reserved.

and ACTIVExtend, in which the effectiveness of ABL treatment in ACTIVE was compared with ALN treatment in ACTIVExtend in postmenopausal women with osteoporosis[61]. Cross-group comparison of the incidence of new vertebral fractures between the ABL group during ACTIVE and the PBO/ALN group during ACTIVExtend showed a significant decrease with initial treatment with ABL versus initial treatment with ALN. These findings further support the use of the anabolic agent prior to the antiresorptive agent in sequential treatment. Both short-term and long-term results

were better with treatment initiated with ABL and followed by ALN, than with primary ALN treatment.

The effectiveness of ABL has been further evaluated by determining the number needed to treat (NNT) to prevent one additional vertebral, nonvertebral, clinical, or major osteoporotic fracture in patients treated with ABL or TPTD using data from ACTIVE[69]. The NNT to prevent one additional vertebral fracture was 28 for ABL and 30 for TPTD based on 18 months of treatment in ACTIVE. The NNT was also lower for ABL versus TPTD for nonvertebral fractures (55 versus 92), clinical fractures (37 versus 59), and major osteoporotic fractures (34 versus 75). These data illustrate the relative efficacy of ABL and TPTD but are specific to the ACTIVE study population.

## Future and ongoing studies

Future studies and ongoing trials with ABL include the collection of real-world data in patients treated with ABL to further establish the effectiveness, safety, and cost of care of ABL in the real-world setting; evaluation of the effects of ABL on indices of bone formation and resorption (NCT03710889); evaluation of the efficacy and safety of ABL in men with osteoporosis (NCT03512262); and evaluation of the efficacy and safety of an intradermal formulation of ABL (NCT01674621), the first anabolic transdermal delivery system for the potential treatment of postmenopausal osteoporosis to begin a phase 3 clinical trial.

## Conclusions

Osteoporosis and associated fractures represent a serious burden on patients and healthcare systems. Despite current treatment options, an unmet need exists in terms of patient education and awareness, diagnosis of osteoporosis, and treatment of patients with osteoporosis.

The results of the ACTIVE trial clearly establish the efficacy and tolerability of ABL across a spectrum of postmenopausal women at high risk of fracture. The results of ACTIVE and ACTIVExtend also demonstrate the efficacy of sequential treatment consisting of initial anabolic treatment with ABL for 18 months to increase bone mass and reduce the risk of vertebral and nonvertebral fractures, followed by treatment with the antiresorptive agent ALN for up to two additional years. The data support a sequential approach to therapy that would start with ABL and be followed by an antiresorptive agent. *Post hoc* analyses of ACTIVE and ACTIVExtend support the safety and efficacy of sequential treatment with ABL followed by ALN in a variety of patient types.

## Transparency

### *Declaration of Funding*

This study was funded by Radius Health, Inc.

### *Declarations of financial/other relationships*

In accordance with Taylor & Francis policy and ethical obligations as researchers, the authors report the following disclosures: P.D.M. is a member of scientific advisory boards for Amgen, and Radius Health, Inc., (Radius; a company that may be affected by the research reported in the enclosed paper. He has disclosed those interests fully to Taylor & Francis, and has in place an approved plan for managing any potential conflicts arising from that involvement), Regeneron, Roche Diagnostics; Takeda Pharmaceutical Company (Takeda), and Ultragenyx. P.D.M. reports serving as a former board member (no longer active) for AgNovos, Alexion, Eli Lilly and Company (Eli Lilly), and Merck and Company. He reports personal fees from Boehringer Ingelheim, Eli Lilly, Immunodiagnostics, Merck and Company, Merck Serono, Roche Holding AG; he reports serving on data safety committees for Allergan and the Grünenthal Group. P.D.M. reports past grants (which are no longer active) from Alexion, Alliance, Amgen, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Immunodiagnostics, Merck, Merck Serono, National Bone Health Alliance, Novartis, Novo Nordisk, Roche Diagnostics, and Radius (a company that may be affected by the research reported in the enclosed paper). J.P.B. is a consultant and speaker for Radius (a company that may be affected by the research reported in the enclosed paper has disclosed those interests fully to Taylor & Francis, and has in place an approved plan for managing any potential conflicts arising from that involvement). J.P.B. is an investigator, consultant, and speaker for Amgen and Takeda; he is a consultant for Regeneron. L.A.F. is a former employee of and owned equity stock in Radius (a company that may be affected by the research reported in the enclosed paper and she has disclosed those interests fully to Taylor & Francis, and has in place an approved plan for managing any potential conflicts arising from that involvement). B.M. is an employee of and owns equity stock in Radius (a company that may be affected by the research reported in the enclosed paper. He has disclosed those interests fully to Taylor & Francis, and has in place an approved plan for managing any potential conflicts arising from that involvement). E.V.M. reports that he and/or his institution has received consultancy fees, and/or research funding, and/or honoraria from AgNovos, Alliance for Better Bone Health, Amgen, Consilient Healthcare, Fresenius Kabi, GE Lunar, GlaxoSmithKline, Hologic, Internis, Lilly, Merck, Novartis, Ono Pharmaceuticals (Ono), Pfizer, Radius (a company that may be affected by the research reported in the enclosed paper; he has disclosed those interests fully to Taylor & Francis, and has in place an approved plan for managing any potential conflicts arising from that involvement); he reports that he and/or his institution has received consultancy fees, and/or research funding, and/or honoraria/speaker fees from AgNovos, Amgen, AstraZeneca, Bayer AG, Consilient Healthcare, Gilead, General Electric, GlaxoSmithKline, Hologic Inc, Eli Lilly, Fresenius Kabi, i3 Innovus, Kyowa Kirin International, Medtronic, Merck Research Labs, Novartis AG, Novo Nordisk, Nycomed, Ono, Pfizer Inc, Radius (a company that may be affected by the research reported in the enclosed paper), Redx Oncology, Roche (F. Hoffmann-La Roche Ltd), Sanofi, Servier Laboratories, Synexus, Tethys, UCB, UBS, ViiV, Warner-Chilcott and Unilever outside the submitted work. F.C. is a consultant, advisor, and speaker for Radius (a company that may be affected by the research reported in the enclosed paper; she has disclosed those interests fully to Taylor & Francis, and has in place an approved plan for managing any potential conflicts arising from that involvement). F.C. is also a consultant, advisor, research grant recipient, and speaker for Amgen and Eli Lilly (no longer active); and an advisor for Merck (no longer active) and consultant for Tarsa/RPharm. H.G.B. is a consultant and speaker for Radius (a company that may be affected by the research reported in the enclosed paper. He has disclosed those interests fully to Taylor & Francis, and has in place an approved plan for managing any potential conflicts arising from that involvement). H.G.B. is an investigator, consultant, and speaker for Amgen and for Takeda, has received research grants from Amgen, has received consulting fees or honoraria from Amgen and Radius (a company that may be affected by the research reported in the enclosed paper); has received payment for lectures and/or speakers bureau from Amgen and Radius (a company that may be affected by the research reported in the enclosed paper), has received support for travel/accommodations from Amgen, and has received payment for development of educational materials from Vindico.

## Author contributions

All authors (P.M.D., J.P.B., L.A.F., B.M., E.V.M., F.C., and H.G.B.) contributed to the drafting of the manuscript and all authors revised it critically for intellectual content. All authors approved the publication of the final manuscript and agree to submission and to be accountable for all aspects of the work.

## Acknowledgements

All listed authors meet the criteria for authorship set forth by the International Committee for Medical Journal Editors. Medical editorial support (Sarah Hummasti, PhD, and Allyson Lehrman, DPM) and graphic services were provided by AOIC, LLC, and were funded by Radius Health, Inc.

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## References

[1] Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis – 2016. Endocr Pract. 2016; 22(Suppl 4):1–42.
[2] Lems WF, Raterman HG. Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs. Ther Adv Musculoskelet Dis. 2017;9(12):299–316.
[3] Office of the Surgeon General (US). Bone health and osteoporosis: a report of the surgeon general. Rockville (MD): Office of the Surgeon General; 2004.
[4] Burge R, Dawson-Hughes B, Solomon DH, et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007;22(3):465–475.
[5] Leader D, Williams S, Curtis J, et al. Osteoporosis-related fracture events in the US [AMCP Nexus Abstract M19]. J Manag Care Spec Pharm. 2017;23(10-a Suppl):S78.
[6] Dempster DW. Osteoporosis and the burden of osteoporosis-related fractures. Am J Manag Care. 2011;17(suppl 6):S164–S169.
[7] Magaziner J, Fredman L, Hawkes W, et al. Changes in functional status attributable to hip fracture: a comparison of hip fracture patients to community-dwelling aged. Am J Epidemiol. 2003; 157(11):1023–1031.
[8] Neuman MD, Silber JH, Magaziner JS, et al. Survival and functional outcomes after hip fracture among nursing home residents. JAMA Intern Med. 2014;174(8):1273–1280.
[9] Cauley JA, Thompson DE, Ensrud KC, et al. Risk of mortality following clinical fractures. Osteoporos Int. 2000;11(7):556–561.
[10] Ensrud KE, Thompson DE, Cauley JA, et al. Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. Fracture Intervention Trial Research Group. J Am Geriatr Soc. 2000;48(3):241–249.
[11] Fink HA, Milavetz DL, Palermo L, et al. What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? J Bone Miner Res. 2005;20(7):1216–1222.
[12] Singer A, Exuzides A, Spangler L, et al. Burden of illness for osteoporotic fractures compared with other serious diseases among postmenopausal women in the United States. Mayo Clin Proc. 2015;90(1):53–62.
[13] Gillespie CW, Morin PE. Osteoporosis-related health services utilization following first hip fracture among a cohort of privately-insured women in the United States, 2008-2014: an observational study. J Bone Miner Res. 2017;32(5):1052–1061.
[14] Lewiecki ME, Wright NC, Curtis JR, et al. Hip fracture trends in the United States, 2002 to 2015. Osteoporos Int. 2018;29(3): 717–722.
[15] Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med. 2007;357(9):905–916.
[16] Pavone V, Testa G, Giardina SMC, et al. Pharmacological therapy of osteoporosis: a systematic current review of literature. Front Pharmacol. 2017;8:803.
[17] van Geel TA, Huntjens KM, van den Bergh JP, et al. Timing of subsequent fractures after an initial fracture. Curr Osteoporos Rep. 2010;8(3):118–122.
[18] Eastell R, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society* clinical practice guideline. J Clin Endocrinol Metab. 2019; 104(5):1595–1622.
[19] Cosman F, Nieves JW, Dempster DW. Treatment sequence matters: anabolic and antiresorptive therapy for osteoporosis. J Bone Miner Res. 2017;32(2):198–202.
[20] Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015; 386(9999):1147–1155.
[21] Jilka RL. Molecular and cellular mechanisms of the anabolic effect of intermittent PTH. Bone. 2007;40(6):1434–1446.
[22] Dean T, Vilardaga JP, Potts JT, Jr, et al. Altered selectivity of parathyroid hormone (PTH) and PTH-related protein (PTHrP) for distinct conformations of the PTH/PTHrP receptor. Mol Endocrinol. 2008;22(1):156–166.
[23] White AD, Fang F, Jean-Alphonse FG, et al. Ca2+ allostery in PTH-receptor signaling. Proc Natl Acad Sci USA. 2019;116(8): 3294–3299.
[24] Ferrandon S, Feinstein TN, Castro M, et al. Sustained cyclic AMP production by parathyroid hormone receptor endocytosis. Nat Chem Biol. 2009;5(10):734–742.
[25] Vilardaga JP, Jean-Alphonse FG, Gardella TJ. Endosomal generation of cAMP in GPCR signaling. Nat Chem Biol. 2014;10(9): 700–706.
[26] Clark LJ, Krieger J, White AD, et al. Allosteric interactions in the parathyroid hormone GPCR-arrestin complex formation. Nat Chem Biol. 2020;16(10):1096–1104.
[27] Calvi LM, Sims NA, Hunzelman JL, et al. Activated parathyroid hormone/parathyroid hormone-related protein receptor in osteoblastic cells differentially affects cortical and trabecular bone. J Clin Invest. 2001;107(3):277–286.
[28] Frolik CA, Black EC, Cain RL, et al. Anabolic and catabolic bone effects of human parathyroid hormone (1-34) are predicted by duration of hormone exposure. Bone. 2003;33(3):372–379.
[29] O'Brien CA, Plotkin LI, Galli C, et al. Control of bone mass and remodeling by PTH receptor signaling in osteocytes. PLOS One. 2008;3(8):e2942.
[30] Varela A, Chouinard L, Lesage E, et al. One year of abaloparatide, a selective activator of the PTH1 receptor, increased bone formation and bone mass in osteopenic ovariectomized rats without increasing bone resorption. J Bone Miner Res. 2017;32(1):24–33.
[31] Hattersley G, Dean T, Corbin BA, et al. Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signaling. Endocrinology. 2016;157(1):141–149.
[32] Bahar H, Gallacher K, Downall J, et al. Six weeks of daily abaloparatide treatment increased vertebral and femoral bone mineral density, microarchitecture and strength in ovariectomized osteopenic rats. Calcif Tissue Int. 2016;99(5):489–499.
[33] Doyle N, Varela A, Haile S, et al. Abaloparatide, a novel PTH receptor agonist, increased bone mass and strength in ovariectomized cynomolgus monkeys by increasing bone formation without increasing bone resorption. Osteoporos Int. 2018;29(3): 685–697.

[34] Varela A, Chouinard L, Lesage E, et al. One year of abaloparatide, a selective peptide activator of the PTH1 receptor, increased bone mass and strength in ovariectomized rats. Bone. 2017;95:143–150.
[35] Makino A, Takagi H, Takahashi Y, et al. Abaloparatide exerts bone anabolic effects with less stimulation of bone resorption-related factors: a comparison with teriparatide. Calcif Tissue Int. 2018; 103(3):289–297.
[36] Ricarte FR, Le Henaff C, Kolupaeva VG, et al. Parathyroid hormone(1-34) and its analogs differentially modulate osteoblastic *Rankl* expression via PKA/SIK2/SIK3 and PP1/PP2A-CRTC3 signaling. J Biol Chem. 2018;293(52):20200–20213.
[37] Mullarkey T, Arlt H, Hu D, et al. Different effects of abaloparatide and hPTH(1-34) on bone resorption and bone formation. Presented at ASBMR 2019. Annual Meeting; 2019 Sept 20–23, Orlando, FL.
[38] Sahbani K, Cardozo CP, Bauman WA, et al. Abaloparatide exhibits greater osteoanabolic response and higher cAMP stimulation and β-arrestin recruitment than teriparatide. Physiol Rep. 2019;7(19): e14225.
[39] Arlt H, Mullarkey T, Hu D, et al. Effects of abaloparatide and teriparatide on bone resorption and bone formation in female mice. Bone Rep. 2020;13:100291.
[40] Burr DB, Hirano T, Turner CH, et al. Intermittently administered human parathyroid hormone(1-34) treatment increases intracortical bone turnover and porosity without reducing bone strength in the humerus of ovariectomized cynomolgus monkeys. J Bone Miner Res. 2001;16(1):157–165.
[41] Sato M, Westmore M, Ma YL, et al. Teriparatide [PTH(1-34)] strengthens the proximal femur of ovariectomized nonhuman primates despite increasing porosity. J Bone Miner Res. 2004;19(4): 623–629.
[42] Fox J, Miller MA, Recker RR, et al. Effects of treatment of ovariectomized adult rhesus monkeys with parathyroid hormone 1-84 for 16 months on trabecular and cortical bone structure and biomechanical properties of the proximal femur. Calcif Tissue Int. 2007;81(1):53–63.
[43] Fox J, Miller MA, Newman MK, et al. Treatment of skeletally mature ovariectomized rhesus monkeys with PTH(1-84) for 16 months increases bone formation and density and improves trabecular architecture and biomechanical properties at the lumbar spine. J Bone Miner Res. 2007;22(2):260–273.
[44] Jolette J, Attalla B, Varela A, et al. Comparing the incidence of bone tumors in rats chronically exposed to the selective PTH type 1 receptor agonist abaloparatide or PTH(1-34). Regul Toxicol Pharmacol. 2017;86:356–365.
[45] Vahle JL, Zuehlke U, Schmidt A, et al. Lack of bone neoplasms and persistence of bone efficacy in cynomolgus macaques after long-term treatment with teriparatide [rhPTH(1-34)]. J Bone Miner Res. 2008;23(12):2033–2039.
[46] Andrews EB, Gilsenan AW, Midkiff K, et al. The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. J Bone Miner Res. 2012;27(12):2429–2437.
[47] Gilsenan A, Harding A, Kellier-Steele N, et al. The Forteo Patient Registry linkage to multiple state cancer registries: study design and results from the first 8 years. Osteoporos Int. 2018;29(10): 2335–2343.
[48] Leder BZ, O'Dea LS, Zanchetta JR, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2015;100(2):697–706.
[49] Bilezikian JP, Hattersley G, Fitzpatrick LA, et al. Abaloparatide-SC improves trabecular microarchitecture as assessed by trabecular bone score (TBS): a 24-week randomized clinical trial. Osteoporos Int. 2018;29(2):323–328.
[50] Miller PD, Hattersley G, Riis BJ, for the ACTIVE Study Investigators, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316(7):722–733.
[51] Bone HG, Cosman F, Miller PD, et al. ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. J Clin Endocrinol Metab. 2018; 103(8):2949–2957.
[52] Cosman F, Miller PD, Williams GC, et al. Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial. Mayo Clin Proc. 2017;92(2):200–210.
[53] Eastell R, Mitlak BH, Wang Y, et al. Bone turnover markers to explain changes in lumbar spine BMD with abaloparatide and teriparatide: results from ACTIVE. Osteoporos Int. 2019;30(3):667–673.
[54] Moreira CA, Fitzpatrick LA, Wang Y, et al. Effects of abaloparatide-SC (BA058) on bone histology and histomorphometry: The ACTIVE phase 3 trial. Bone. 2017;97:314–319.
[55] Greenspan S, Fitzpatrick LA, Mitlak B, et al. Abaloparatide followed by alendronate in women ≥80 years with osteoporosis: *post hoc* analysis of ACTIVExtend. Menopause. 2020;27(10): 1137–1142.
[56] Watts NB, Hattersley G, Fitzpatrick LA, et al. Abaloparatide effect on forearm bone mineral density and wrist fracture risk in postmenopausal women with osteoporosis. Osteoporos Int. 2019; 30(6):1187–1194.
[57] Bilezikian JP, Hattersley G, Mitlak B, et al. Abaloparatide in patients with mild or moderate renal impairment: results from the ACTIVE phase 3 trial. Curr Med Res Opin. 2019;35(12): 2097–2102.
[58] Miller PD, Hattersley G, Lau E, et al. 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. Bone. 2019;120:137–140.
[59] Dhaliwal R, Hans D, Hattersley G, et al. Abaloparatide in postmenopausal women with osteoporosis and type 2 diabetes: a *post-hoc* analysis of the ACTIVE study. JBMR Plus. 2020;4(4):e10346.
[60] McCloskey EV, Fitzpatrick LA, Hu MY, et al. Effect of abaloparatide on vertebral, nonvertebral, major osteoporotic, and clinical fractures in a subset of postmenopausal women at increased risk of fracture by FRAX probability. Arch Osteoporos. 2019;14(1):15.
[61] Leder BZ, Mitlak B, Hu M, et al. Effect of abaloparatide vs alendronate on fracture risk reduction in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2020;1(3):105.
[62] 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(8):1625–1631.
[63] McClung MR, Harvey NC, Fitzpatrick LA, et al. Effects of abaloparatide on bone mineral density and risk of fracture in postmenopausal women aged 80 years or older with osteoporosis. Menopause. 2018;25:767–771.
[64] Cosman F, Hattersley G, Hu MY, et al. Effects of abaloparatide-SC on fractures and bone mineral density in subgroups of postmenopausal women with osteoporosis and varying baseline risk factors. J Bone Miner Res. 2017;32(1):17–23.
[65] Watts NB, Dore RK, Baim S, et al. Forearm bone mineral density and fracture incidence in postmenopausal women with osteoporosis: results from the ACTIVExtend phase 3 trial [ASBMR abstract 0941]. J Bone Miner Res. 2018;33(S1):S292.
[66] Leder BZ, Zapalowski C, Hu M, et al. Fracture and bone mineral density response by baseline risk in patients treated with abaloparatide followed by alendronate: results from the phase 3 ACTIVExtend trial. J Bone Miner Res. 2019; 34(12):2213–2219.
[67] McClung MR, Williams GC, Hattersley G, et al. Geography of fracture incidence in postmenopausal women with osteoporosis treated with abaloparatide. Calcif Tissue Int. 2018;102(6):627–633.
[68] Deal CL, Mitlak BH, Wang Y, et al. 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. Bone Rep. 2019;11(11):100230.
[69] Reginster JY, Hattersley G, Williams GC, et al. Abaloparatide is an effective treatment option for postmenopausal osteoporosis: review of the number needed to treat compared with teriparatide. Calcif Tissue Int. 2018;103(5):540–545.