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ORIGINAL ARTICLE

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

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Abstract

Objective: To assess the efficacy and safety of 18 months of subcutaneous abaloparatide (ABL-SC) or placebo (PBO) followed by 6 months of alendronate (ALN) (preplanned interim analysis).

Patients and Methods: ACTIVExtend, an extension of ACTIVE, enrolled patients who completed 18 months of ABL-SC or PBO in ACTIVE to receive up to 24 additional months of open-label ALN; there was 1 month between the studies to re-consent patients.

Results: Of 1243 eligible ACTIVE patients, 1139 (92%) were enrolled in ACTIVExtend beginning November 20, 2012. These results are from a prespecified 6-month interim analysis (cutoff date, June 2, 2015); the study is ongoing. Findings indicated percentages of patients with new morphometric vertebral fractures: PBO/ALN, 4.4% vs ABL-SC/ALN, 0.55%; relative risk reduction, 87% (relative risk, 0.13; 95% CI, 0.04-0.41; $P<.001$). Kaplan-Meier estimated rates of nonvertebral fractures were PBO/ALN, 5.6% vs ABL-SC/ALN, 2.7%; risk reduction, 52% (hazard ratio [HR], 0.48; 95% CI, 0.26-0.89; log-rank $P=.02$). There was also a 58% risk reduction of major osteoporotic fractures (HR, 0.42; 95% CI, 0.21-0.85; log-rank $P=.01$) and a 45% risk reduction of clinical fractures (HR, 0.55; 95% CI, 0.33-0.92; log-rank $P=.02$) in the ABL-SC/ALN group vs the PBO/ALN group. At 25 months, bone mineral density percentage change from ACTIVE baseline for ABL-SC/ALN vs PBO/ALN was as follows: lumbar spine, 12.8%; total hip, 5.5%; femoral neck, 4.5% vs 3.5%, 1.4%, 0.5%, respectively (group differences at all sites $P<.001$).

Conclusion: Use of ABL-SC for 18 months followed by ALN for 6 months improved bone mineral density and reduced fracture risk throughout the skeleton and may be an effective treatment option for postmenopausal women with osteoporosis.

Trial Registration: clinicaltrials.gov Identifier: NCT01657162.

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Only one osteoanabolic agent (teriparatide [TPTD], the 34–amino acid terminal peptide of parathyroid hormone [PTH]) is currently marketed worldwide. Teriparatide significantly reduces the risk of vertebral and nonvertebral fractures over 18 months.[1] Despite the clear efficacy of this agent, there does not seem to be an early separation in the incidence of nonvertebral fractures between the TPTD- and placebo (PBO)-treated groups: Kaplan-Meier incidence curves do not begin to diverge until after 9 to 10 months of treatment.[1] This is important for patients with recent fractures, who are at very high risk for additional fractures,[2,3] particularly during the first year after fracture.[4-12] Therefore, osteoanabolic agents

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with more rapid onset of action for the prevention of nonvertebral fractures are needed.

Abaloparatide (ABL) is a peptide designed by strategic insertion of residues into the parathyroid hormone PTH-related peptide amino-terminal fragment between residues 22 and 34. The resulting peptide is a selective activator of the PTH type 1 receptor signaling pathway with the ability to produce anabolic effects with modest stimulation of bone resorption compared with TPTD.[13] This ability seems to be due to unique interactions with the PTH type 1 receptor, in which lower-affinity binding to the "resorptive" R^0 configuration of the receptor (with maintained high-affinity binding to the bone formation configuration of the receptor) results in less calcium mobilization than PTH or PTH-related peptide and a net greater anabolic effect.[14,15] Phase 2 study findings suggested that subcutaneously administered ABL (ABL-SC) produces rapid bone mineral density (BMD) increments in the lumbar spine (LS) and at primarily cortical skeletal sites, including the hip, that were significantly higher than those produced by TPTD.[16] Phase 3 study results from the ACTIVE trial (Abaloparatide Comparator Trial In Vertebral Endpoints) indicate that ABL-SC treatment for 18 months reduced new morphometric vertebral fractures by 86% and nonvertebral fractures by 43%, with rapid separation in nonvertebral fracture risk between the ABL-SC and PBO groups.[17]

Osteoanabolic treatment is most appropriate for patients who have already experienced osteoporosis-related fractures or who have very low BMD or other risk factors. In these patients, substantial quantitative and microstructural skeletal deficits are more likely to be improved or reversed with anabolic therapy compared with antiresorptive therapy.[18-20] Treatment duration with current anabolic therapy is limited to 18 to 24 months, and skeletal improvements from anabolic agents require subsequent antiresorptive therapy to be maintained; in the absence of subsequent antiresorptive treatment, the BMD benefits will gradually be lost.[21-23] In contrast, in the presence of an antiresorptive treatment, such as alendronate (ALN) or denosumab, after TPTD treatment, bone mass benefits persist or increase significantly.[21,24-26] Therefore, anabolic therapy followed by transitioning to an antiresorptive agent seems to be an attractive treatment strategy for patients with osteoporosis.

The present study, an extension trial of ACTIVE (ACTIVExtend), was designed to determine the efficacy and safety of 18 months of daily ABL-SC compared with PBO, followed by oral, open-label ALN for an additional 24 months for the treatment of women with postmenopausal osteoporosis. The main objectives of this study were to compare the incidence of new morphometric vertebral and nonvertebral fractures in patients receiving sequential ABL-SC followed by ALN (ABL-SC/ALN) compared with sequential PBO followed by ALN (PBO/ALN) in a preplanned interim analysis after 6 months of ALN. The objectives also included evaluation of group differences in BMD and safety.

METHODS

Study Design

In ACTIVE, postmenopausal women with osteoporosis were randomized 1:1:1 to receive blinded daily injections of ABL-SC 80 μg or matching injections of PBO or open-label daily injections of TPTD 20 μg for 18 months.[17] The PBO and ABL-SC arms were continued on active treatment, ALN, to examine the long-term safety of the use of ABL-SC and to allow the PBO-treated participants to receive an active osteoporosis treatment. In ACTIVExtend, eligible women who were previously randomized to receive either blinded ABL-SC or blinded PBO were invited to enter the extension trial in which all participants were treated with open-label ALN 70 mg orally once per week for 24 months. Between the final ACTIVE visit and the initiation of ACTIVExtend, there was a 1-month period dedicated to recruiting and consenting patients to ACTIVExtend. Two different baselines were used to describe study findings depending on the type of analysis. The integrated ACTIVE and ACTIVExtend efficacy analyses used 25 months of data from month 0 of ACTIVE (baseline) through month 6 of ACTIVExtend. For the safety analysis and exploratory efficacy end points, month 0 of ACTIVExtend (which was approximately 1 month after the month 18 visit in ACTIVE) was used as baseline unless otherwise specified. This is a report of the results of the 6-month planned interim analysis (cutoff date, June 2, 2015) of ACTIVExtend

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(month 25). The study was conducted in accordance with the ethical principles contained in the Declaration of Helsinki and is in compliance with Good Clinical Practice guidelines and all other applicable local regulatory and ethical requirements.

Study Participants

The multicenter, multinational ACTIVE trial enrolled 2463 postmenopausal women (aged 49-86 years) and compared 18 months of ABL-SC with PBO and TPTD. Women 65 years and younger who had previous radiographic evidence of vertebral fracture at any time or who had a nonvertebral fracture within 5 years of study enrollment were eligible if they also had a BMD T-score of −2.5 or less but greater than −5.0 at the LS or femoral neck (FN). Women older than 65 years who met these fracture criteria could enroll if their LS or FN BMD T-score was −2.0 or less and greater than −5.0. Women older than 65 years could also be enrolled, even if they did not meet the fracture criteria, if their LS or FN BMD T-score was −3.0 or less and greater than −5.0. Women in the blinded ABL-SC and blinded PBO groups in ACTIVE who completed the 18-month end-of-treatment visit, were more than 80% compliant with study medication during ACTIVE, and, in the opinion of the investigators, were appropriate candidates for treatment with ALN, were offered participation in ACTIVExtend. Women were excluded if they had experienced a treatment-related serious adverse event (AE), had stopped taking study medication, were noncompliant, or had withdrawn from ACTIVE for any reason. The end-of-treatment visit in ACTIVE served as the first visit for ACTIVExtend. Of the 1243 women who completed the ABL-SC or PBO arm of ACTIVE, 1139 (92%) were enrolled in ACTIVExtend beginning November 20, 2012. Figure 1 shows the disposition of patients for ACTIVExtend.

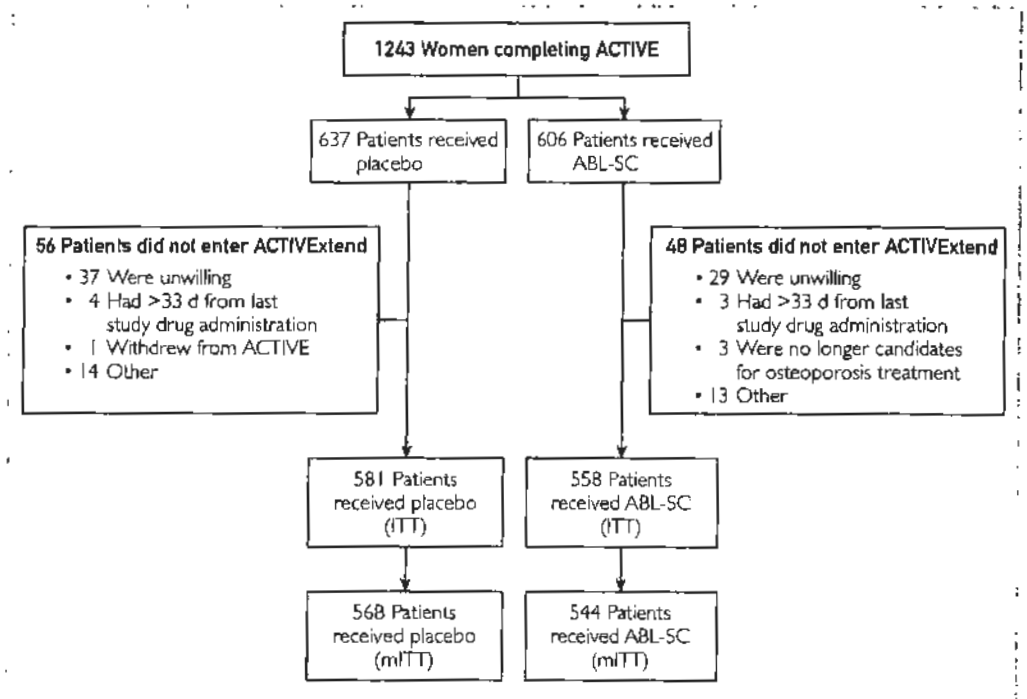

FIGURE 1. Disposition of patients in ACTIVExtend (extension trial of the Abaloparatide Comparator Trial in Vertebral Endpoints [ACTIVE]). The treatment groups are based on randomization in ACTIVE. The populations shown are intention-to-treat (ITT) and patients with evaluable spinal radiographs in ACTIVE and at the 6-month ACTIVExtend visit (modified ITT [mITT]). All the patients in ACTIVExtend received alendronate. ABL-SC = subcutaneous abaloparatide.

Randomization and Masking

Efficacy and safety were analyzed according to the ACTIVE double-blind randomized assignment to receive either ABL-SC or PBO. The study personnel and participants remained blinded to the initial treatment group assignment in ACTIVE while patients were receiving open-label ALN 70 mg weekly during the first 6 months of therapy. All the participants received supplements of elemental calcium 500 to 1000 mg/d and vitamin D 400 to 800 IU based on the local standard of care.

Efficacy End Points

The primary end point was the percentage of participants who sustained 1 or more new morphometric vertebral fractures between the baseline of ACTIVE and 6 months after the initiation of ALN in the ABL-SC/ALN group vs the PBO/ALN group. An exploratory outcome was the percentage of patients with 1 or more new morphometric vertebral fractures between the baseline of ACTIVExtend (ie, the ACTIVE end-of-treatment 18-month visit) and 6 months into the extension study. Anteroposterior and lateral radiographs of the lumbar and thoracic spine were obtained for these analyses. The radiographs were assessed by a radiologist (BioClinica-Synarc) blinded to ACTIVE randomized treatment assignment, and new morphometric vertebral fractures were assessed according to the semiquantitative methods of Genant et al.[27] A second radiologist reviewed radiographs in which an incident fracture had been identified to confirm the reading; if necessary, a third assessment adjudicated the incident fracture.

Secondary end points included the incidence and time to first event for nonvertebral, major osteoporotic, and clinical fractures. Nonvertebral fractures were defined as clinical fractures associated with low trauma, such as a fall from standing height or off of 1 step, such as a curb. Such fractures excluded pathologic fractures and those of the toes, fingers, skull, face, sternum, and patella (per US Food and Drug Administration guidance). Nonvertebral fractures were initially self-reported and then adjudicated with confirmatory source documents, and treatment assignments remained blinded. Major osteoporotic fractures were defined as fractures of the clinical spine, forearm, hip, or shoulder, irrespective of the level of trauma. Clinical fractures were defined as all fractures that would cause a patient to seek medical care, regardless of level of trauma.

Additional secondary end points included percentage change in LS, total hip (TH), and FN BMD assessed from the baseline of ACTIVE to 6 months of ACTIVExtend and, in a subset of patients, changes in serum markers of bone turnover (procollagen type I N-terminal propeptide [s-PINP] and carboxy-terminal cross-linking telopeptide of type I collagen [s-CTX]; COBAS 411 robot, Roche Diagnostics GmbH). The BMD was measured by dual-energy x-ray absorptiometry using approved scanners (Hologic or GE Healthcare Lunar); for each patient, the same scanner was to be used for all evaluations of BMD. If a scanner was changed during the course of the study, adjustments were made to calibrate differences between the old and new scanner (BioClinica-Synarc).

Safety

The safety experience for ABL-SC, PBO, and TPTD over 18 months in ACTIVE was previously described elsewhere.[17] Safety evaluations included herein are those from the first 6 months of ACTIVExtend only and include a physical examination, electrocardiogram, and clinical laboratory tests after 6 months of ALN, as well as monitoring and reporting of AEs at each study visit (3 and 6 months). Patients were withdrawn from the study if they had a confirmed substantial deterioration in BMD (>7% decrease from baseline of ACTIVExtend at the LS, TH, or FN), treatment-related serious AEs, refusal of treatment, or the inability to complete the study procedures or if they were lost to follow-up. All treatment-emergent AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.1.

Statistical Analyses

The statistical analyses were specified in a statistical analysis plan that was finalized before the unblinding of original treatment assignments and data analyses. Because ACTIVExtend is an extension study, no additional formal sample size analysis was performed. The primary and secondary end points were analyzed with integrated data using the baseline data from ACTIVE. Safety and several

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exploratory end points were analyzed using the baseline data from ACTIVExtend.

Patients from ACTIVE who were not subsequently enrolled in ACTIVExtend were excluded from the data analyses. All the efficacy analyses except those for vertebral fracture were based on an intention-to-treat (ITT) population including all patients in ACTIVE who were enrolled in ACTIVExtend. The population used for the analyses of vertebral fractures included patients in ACTIVE with evaluable spinal radiographs at baseline and 18 months who also had evaluable spinal radiographs at the ACTIVExtend 6-month visit. The association between new morphometric vertebral fractures and the 2 treatment groups was assessed using a Fisher exact test. Times to first nonvertebral, major osteoporotic, and clinical fractures were analyzed using the Kaplan-Meier method and were compared across groups using a log-rank test. Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% CIs. The percentage change in BMD for the LS, TH, and FN was analyzed using an analysis of covariance model, with missing data imputed based on the last observation carried forward. Biochemical markers of bone turnover were analyzed in the subset of patients who had this measurement in ACTIVE and had at least 1 measurement in ACTIVExtend. This was based on the ratio of the 6-month value in ACTIVExtend relative to baseline in ACTIVE using a log transformation to normalize the distribution and then using analysis of covariance. Safety was evaluated in all intention-to-treat patients who received at least 1 dose of ALN.

A hierarchical approach[28] using fixed-sequence testing was used to control the overall type 1 error rate at the 2-sided significance level of 5% for testing ABL-SC/ALN vs PBO/ALN for the following end points: vertebral fractures; TH, FN, and LS BMD; and nonvertebral, clinical, and major osteoporotic fractures. Statistical testing was performed sequentially as long as statistical significance at the 5% level was attained at each step.

RESULTS

Table 1 illustrates key demographic and baseline characteristics for participants. Overall, the PBO/ALN and ABL-SC/ALN groups were well matched. At the baseline of ACTIVE, the mean age was 68.6 years, 22% of participants had a prevalent vertebral fracture, 49% reported a history of nonvertebral fracture, and 39% had no previous fracture before enrolling in ACTIVE. There were no clinically meaningful differences in baseline characteristics between the ACTIVExtend cohort and the full ACTIVE cohort. At the baseline of ACTIVExtend, mean LS and TH BMD T-scores were −2.11 and −1.63 in the ABL-SC/ALN group and −2.87 and −1.93 in the PBO/ALN group, respectively, consistent with the gains in BMD associated with ABL-SC treatment vs PBO in the ACTIVE trial.

TABLE 1. Demographic and Baseline Characteristics of the ACTIVExtend Population[a]

Characteristic	PBO/ALN Group (n=581)[b]	ABL-SC/ALN Group (n=558)[b]
Age[c]		
Mean (y), mean ± SD	68.5±6.3	68.6±6.5
Group (No. [%])		
<65 y	114 (19.6)	106 (19.0)
65 to <75 y	370 (63.7)	351 (62.9)
≥75 y	97 (16.7)	101 (18.1)
Body mass index (mean ± SD)	24.96±3.50	24.93±3.49
Race/ethnicity (No. [%])		
Asian	106 (18.2)	101 (18.1)
Black	18 (3.1)	19 (3.4)
White	447 (76.9)	433 (77.6)
Other race	10 (1.7)	5 (0.9)
Hispanic or Latino	139 (23.9)	124 (22.2)
Prevalent vertebral fracture (No. [%])	132 (22.8)[d]	121 (21.7)
Previous nonvertebral fracture (No. [%])	282 (48.5)	272 (48.7)
No history of fracture (No. [%])	231 (39.8)	207 (37.1)

[a]ABL-SC = subcutaneous abaloparatide; ACTIVExtend = extension trial of the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE); ALN = alendronate; PBO = placebo.
[b]Treatment groups are based on randomization in ACTIVE. Baseline and demographic characteristics are based on ACTIVE baseline.
[c]Age was calculated from the date of ACTIVE randomization.
[d]Based on 580 patients.

Fracture risk reduction

Fracture results for vertebral and nonvertebral fractures are shown in Figure 2, A and B, respectively. During the first 6 months of ACTIVExtend, there were 7 new morphometric vertebral fractures in the PBO/ALN group and 0 in the ABL-SC/ALN group. New morphometric vertebral fractures over 25 months occurred in 4.4% of the PBO/ALN group vs 0.55% of the ABL-SC/ALN group,

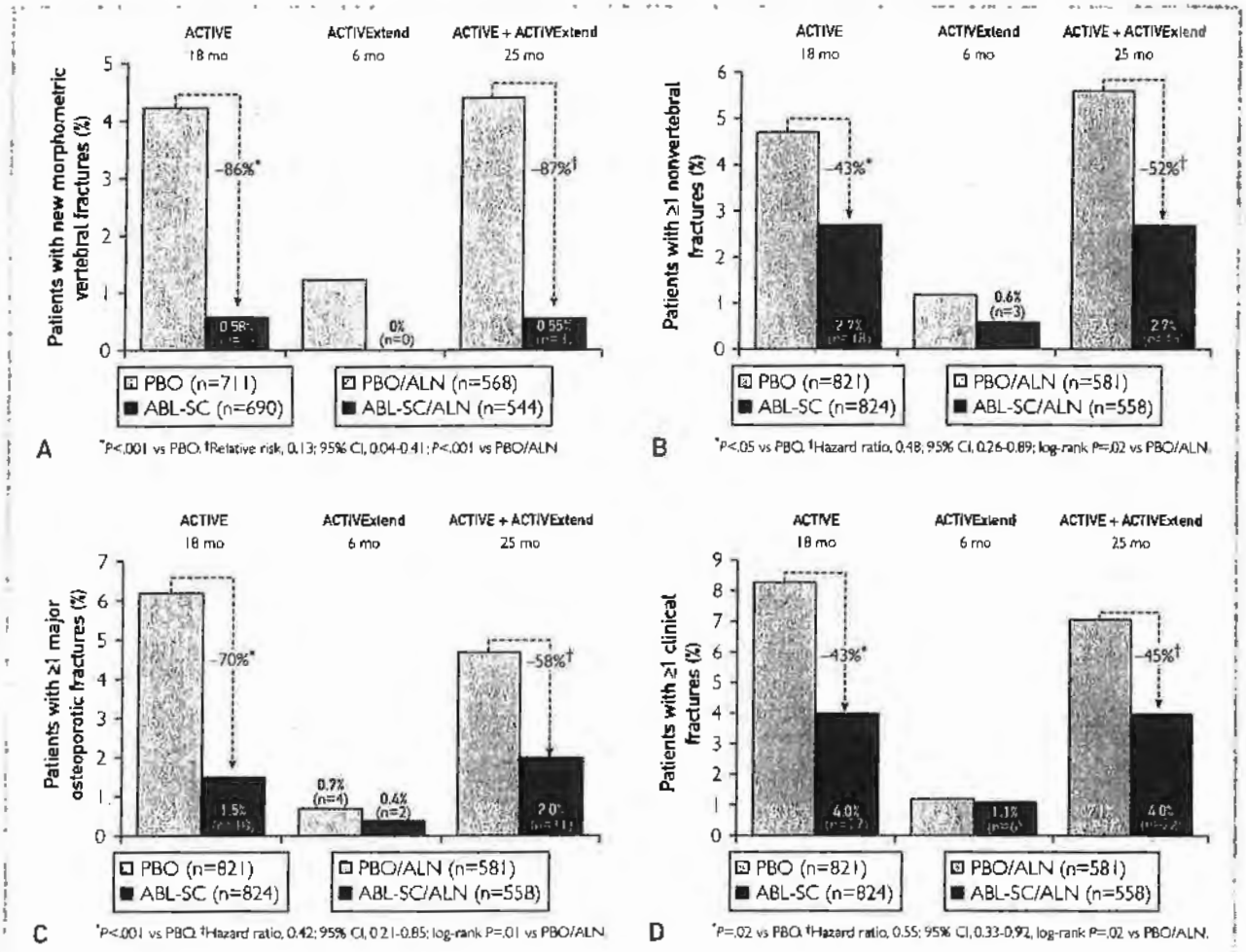

FIGURE 2. Risk reduction of fractures: incidence of new morphometric vertebral fractures (A) and Kaplan-Meier estimated event rates for nonvertebral (B), major osteoporotic (C), and clinical (D) fractures from month 0 to month 6 of ACTIVExtend (extension trial of the Abaloparatide Comparator Trial In Vertebral Endpoints [ACTIVE]) and cumulatively from baseline of ACTIVE to month 6 of ACTIVExtend (25 study months total). In ACTIVE, patients received 18 months of subcutaneous abaloparatide (ABL-SC) or placebo (PBO); in ACTIVExtend, former ABL-SC and former PBO patients all received alendronate (ALN) after a 1-month recruitment period. Data from the 18-month ACTIVE trial are presented for context.[17]

representing an 87% relative risk reduction for new morphometric vertebral fractures (relative risk, 0.13; 95% CI, 0.04-0.41; P<.001). There were 7 nonvertebral fractures during the first 6 months of ACTIVExtend in the PBO/ALN group and 3 in the ABL-SC/ALN group. The 25-month Kaplan-Meier estimated rates were 5.6% vs 2.7% in the groups, respectively, representing a 52% risk reduction in the incidence of nonvertebral fractures for the ABL-SC/ALN group (HR, 0.48; 95% CI, 0.26-0.89; log-rank P=.02). The initial separation of incidence on the Kaplan-Meier curve during ACTIVE continued into ACTIVExtend (Figure 3A).

Major osteoporotic fractures and clinical fractures are shown in Figure 2, C and D, respectively. There were 4 major osteoporotic fractures in the PBO/ALN group and 2 in the ABL-SC/ALN group during the 6-month extension period. The 25-month Kaplan-Meier estimated rates were 4.7% in the PBO/ALN group vs 2.0% in the ABL-SC/ALN group during the first 6 months of ACTIVExtend, representing a 58% risk reduction for major osteoporotic fractures in the ABL-SC/ALN

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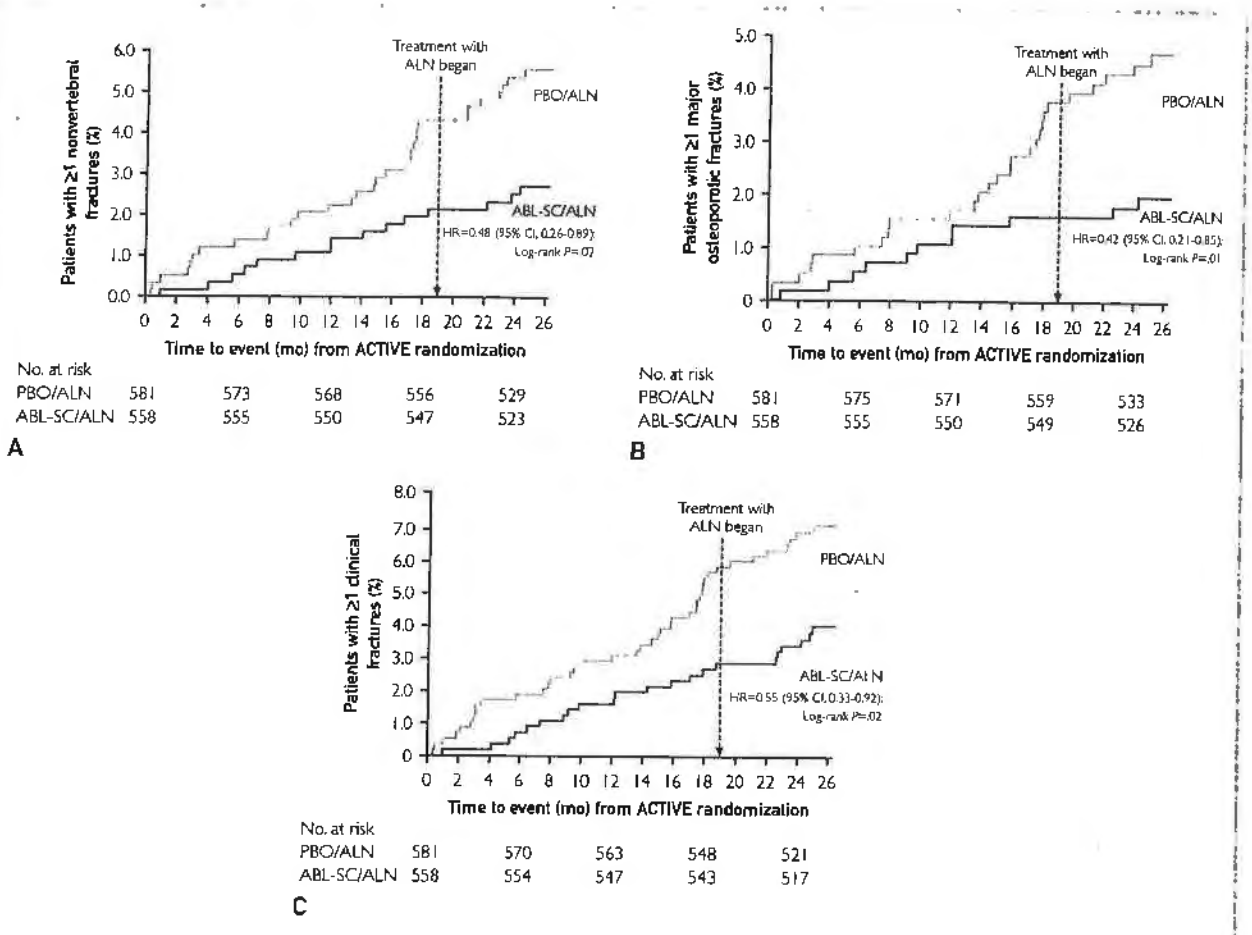

FIGURE 3. Kaplan-Meier curves of time to first incident nonvertebral (A), major osteoporotic (B), and clinical (C) fracture from ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints) baseline through 6 months of ACTIVExtend (extension trial of ACTIVE). ABL-SC = subcutaneous abaloparatide; ALN = alendronate; HR = hazard ratio; PBO = placebo.

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group (HR, 0.42; 95% CI, 0.21-0.85; log-rank P=.01). There was an early separation in the incidence of major osteoporotic fracture in the ABL-SC/ALN and PBO/ALN groups, with continued divergence over time (Figure 3B). There was also a prolonged time to first clinical fracture (Figure 3C) in the ABL-SC/ALN group vs the PBO/ALN group through the first 25 months, with a 45% reduction in risk (HR, 0.55; 95% CI, 0.33-0.92; log-rank P=.02).

BMD. The BMD percentage changes from ACTIVE baseline over 25 months are shown in Figure 4. Average gains for the ABL-SC/ALN group vs the PBO/ALN group were 12.8% vs 3.5% for LS, 5.5% vs 1.4% for TH, and 4.5% vs 0.5% for FN (P<.001 group differences for each site).

Serum bone markers

At the end of ACTIVE, in the ABL-SC group, the mean concentrations of s-PINP and s-CTX increased compared to baseline 94.6% and 19.6%, respectively. From the introduction of ALN at month 0 of ACTIVExtend to month 6, mean concentrations of s-PINP declined 54.2% in the ABL-SC/ALN and PBO/ALN groups combined, and mean concentrations of s-CTX declined 63.9% in both groups combined. There were no between-group differences in concentrations of either marker after 6 months of ALN (cumulative month 25; data not shown).

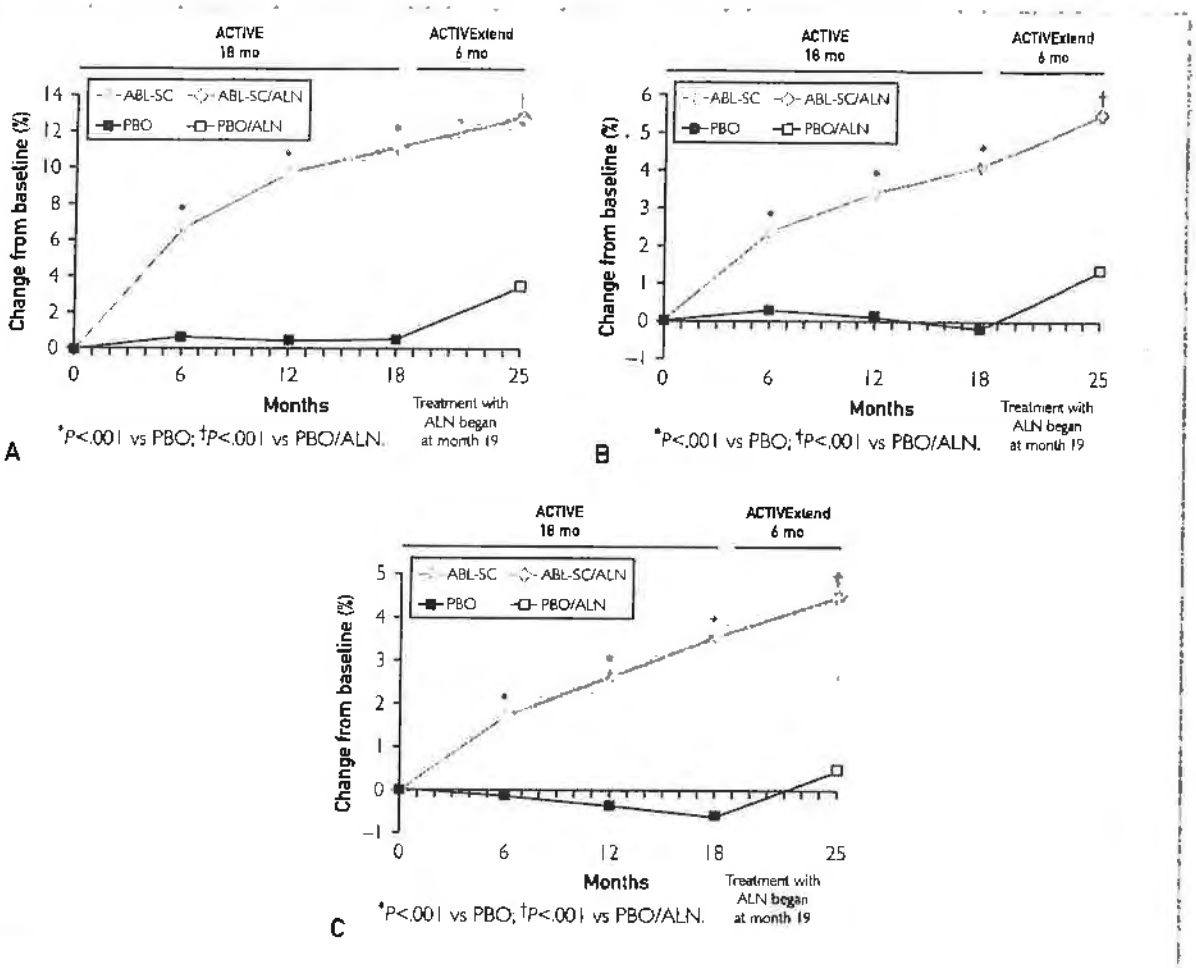

FIGURE 4. Changes in bone mineral density (BMD) over 25 months. Mean percentage change in lumbar spine (A), total hip (B), and femoral neck (C) BMD from baseline of ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints) to the 6-month visit of ACTIVExtend (extension trial of ACTIVE) in the ACTIVExtend intention-to-treat population, using last observation carried forward. ABL-SC = subcutaneous abaloparatide; ALN = alendronate; PBO = placebo.

Safety

Table 2 shows AEs during the first 6 months of ACTIVExtend for the ABL-SC/ALN and PBO/ALN groups. As expected, with all patients taking ALN during this extension study, there were no differences between groups. The only treatment-emergent AE that occurred in more than 4% of the population was arthralgia, and the incidence was similar between groups. During the first 6 months of ACTIVExtend, there were no reports of hypercalcemia as an AE; there was 1 report of "blood calcium increased" as a treatment-emergent AE in the ABL-SC/ALN group.

DISCUSSION

The ACTIVExtend study adds to findings from the ACTIVE trial. In ACTIVE, 18 months of ABL-SC treatment reduced new morphometric vertebral fractures by 86%, nonvertebral fractures by 43%, clinical fractures by 43%, and major osteoporotic fractures by 70%.[17] The study was extended 24 months by switching the PBO and ABL-SC arms in ACTIVE to ALN (ACTIVExtend). By the first 6 months of ACTIVExtend, a 25-month sequential treatment with 18 months of ABL-SC, a 1-month interval to obtain consent, and 6 months of ALN reduced the risk of new morphometric

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vertebral fractures by 87% and nonvertebral fractures by 52% compared with the sequential administration of PBO followed by 6 months of ALN. A statistically significant risk reduction in the ABL-SC/ALN group compared with the PBO/ALN group was also demonstrated for major osteoporotic fractures and clinical fractures. The BMD increases in the ABL-SC/ALN group were 12.8%, 5.5%, and 4.5% for the LS, TH, and FN, respectively. There were no differences between groups at the end of the 6-month extension in bone turnover markers and no differences in safety end points during the extension study.

The use of ALN after ABL-SC administration in ACTIVExtend provides a formal assessment of a real-world therapeutic scenario for patients with postmenopausal osteoporosis. Patients usually require antiresorptive treatment after anabolic therapy to preserve osteoanabolic benefits. The observation that there were significantly fewer vertebral and nonvertebral fractures during 6 months of ALN treatment in the group that was originally randomized to receive ABL-SC suggests there is a persistent effect of ABL-SC on improving bone strength. Findings from this study support early anabolic therapy as a potential treatment option for qualified postmenopausal women with osteoporosis. Because most patients with previous fractures or very low BMD have structural and quantitative deficits in skeletal integrity, anabolic treatment to repair these defects is desirable.[29-31] Furthermore, the sequence of anabolic therapy followed by antiresorptive therapy may have the greatest chance of achieving increases in BMD and reaching the goal of preventing fractures. Attainment of BMD goals is likely to take much longer or to fail for many patients with long-term antiresorptive therapy alone.[32-34]

There are still several unanswered questions about the potential use of treatment with ABL-SC followed by antiresorptive therapy. One is whether a different antiresorptive agent can be substituted for ALN and still produce the therapeutic benefits shown in ACTIVExtend. Based on experience with TPTD followed by agents such as zoledronic acid and denosumab, it is probable that these antiresorptive agents would be at least as likely as ALN to preserve the osteoanabolic benefits of ABL-SC.[26,35] Second, will the benefits of ABL-SC therapy be maintained through a full 2 years of subsequent antiresorptive treatment? We will determine the answers to this question at the end of ACTIVExtend, when all the participants will have completed a full 24-month course of ALN after the original 18 months of ABL-SC or PBO. Third, is it possible to use ABL-SC after previous antiresorptive therapy rather than as first-line treatment and obtain similar benefits? This needs to be addressed in a separate study; BMD increments with TPTD after antiresorptive treatment are not as high, particularly in the hip region, as they are when TPTD is used as first-line treatment.[36] And fourth, can the findings from ACTIVE and ACTIVExtend apply to other populations? This trial enrolled only postmenopausal women with osteoporosis, and the results cannot be extrapolated to other populations, such as men, premenopausal women, or patients with specific causes of bone loss, such as those who have received organ transplants or glucocorticoid therapy.

TABLE 2. AEs Reported During the First 6 Months of ACTIVExtend[a]

AE	PBO/ALN Group (No. [%]) (n=580)[b]	ABL-SC/ALN Group (No. [%]) (n=553)[b]
All AEs[c]	469 (80.9)	447 (80.8)
Serious AEs	25 (4.3)	21 (3.8)
AEs leading to death	1 (0.2)	1 (0.2)
AEs leading to discontinuation	22 (3.8)	18 (3.3)
All TEAEs	319 (55.0)	301 (54.4)
Common (>2% overall) TEAEs		
Arthralgia	27 (4.7)	24 (4.3)
Upper respiratory tract infection	26 (4.5)	14 (2.5)
Dyspepsia	13 (2.2)	15 (2.7)
Abdominal pain, upper	15 (2.6)	10 (1.8)

[a]ABL-SC = subcutaneous abaloparatide; ACTIVExtend = extension trial of the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE); AE = adverse event; ALN = alendronate; PBO = placebo; TEAE = treatment-emergent adverse event.

[b]Treatment groups are based on randomization in ACTIVE. The population includes all patients enrolled in ACTIVExtend who received 1 or more doses of ALN.

[c]Includes AEs that either started on or after ACTIVExtend visit 1 or were ongoing at ACTIVExtend visit 1.

CONCLUSION

The sequence of ABL-SC followed by 6 months of ALN improved BMD and reduced fracture risk throughout the skeleton and is likely to be a highly effective treatment option

for postmenopausal women at risk for osteoporosis-related fractures.

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Abbreviations and Acronyms: **ABL-SC** = subcutaneous abaloparatide; **ACTIVE** = Abaloparatide Comparator Trial In Vertebral Endpoints; **ACTIVExtend** = extension trial of the Abaloparatide Comparator Trial In Vertebral Endpoints; **AE** = adverse event; **ALN** = alendronate; **BMD** = bone mineral density; **FN** = femoral neck; **HR** = hazard ratio; **ITT** = intention-to-treat; **LS** = lumbar spine; **mITT** = modified ITT; **PBO** = placebo; **PTH** = parathyroid hormone; **s-CTX** = serum carboxy-terminal cross-linking telopeptide of type I collagen; **s-PINP** = serum procollagen type I N-terminal propeptide; **TEAE** = treatment-emergent adverse event; **TH** = total hip; **TPTD** = teriparatide

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