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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 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