ASBMR
The American Society for
Bone and Mineral Research

OXFORD

Response rates for lumbar spine, total hip, and femoral neck bone mineral density in men treated with abaloparatide: results from the ATOM study

Ruban Dhaliwal[1], David Kendler[2], Kenneth Saag[3], Steven W. Ing[4], Andrea Singer[5],
Robert A. Adler[6], Leny Pearman[7], Yamei Wang[8], Bruce Mitlak[9],* [iD]

[1]Metabolic Bone Disease Center, State University of New York Upstate Medical University, Syracuse, NY 13210, United States
[2]Division of Endocrinology, University of British Columbia, Vancouver, BC V6T 1Z4, Canada
[3]Division of Clinical Immunology and Rheumatology, The University of Alabama at Birmingham, Birmingham, AL 35294, United States
[4]Department of Internal Medicine, Ohio State University Wexner Medical Center, Columbus, OH 43210, United States
[5]Department of Obstetrics and Gynecology, MedStar Georgetown University Hospital, Washington, DC 20007, United States
[6]Department of Endocrinology and Metabolism at the Department of Veteran's Affairs, Richmond Veterans Affairs Medical Center-Richmond, VA 23249, United States
[7]Medical Affairs, Radius Health, Inc., Boston, MA 02210, United States
[8]Department of Biostatistics, Radius Health, Inc., Boston, MA 02210, United States
[9]Discovery Sciences, Radius Health, Inc., Boston, MA 02210, United States

*Corresponding author: Bruce Mitlak, Discovery Sciences, Radius Health, Inc., 22 Boston Wharf Rd, Boston, MA 02210, United States. (bmitlak@radiuspharm.com).

Abstract

Osteoporosis in men is an underappreciated public health issue, accounting for approximately 30% of the societal burden of osteoporosis. Although the prevalence of osteoporosis in men is lower, fracture-related morbidity and mortality rates exceed those of women. Abaloparatide is a synthetic, 34-amino acid peptide with homology to human parathyroid hormone-related protein (PTHrP), which favors bone formation by selective activation of PTH receptor type 1. In the Abaloparatide for the Treatment of Men With Osteoporosis (ATOM; NCT03512262) trial, 228 men with primary or hypogonadism-associated osteoporosis were randomized to receive subcutaneous injections of abaloparatide 80 μg or placebo. Abaloparatide significantly improved LS, TH, and FN BMD when compared with placebo. In this prespecified analysis, the proportion of men with a percent change from baseline of >0%, >3%, and >6% in BMD at the LS, TH, and FN at 3, 6, and 12 mo and/or a shift in T-score category (based on LS and TH T-scores) at 12 mo was compared between the abaloparatide and placebo groups in ATOM. There were significantly more men with a BMD gain of >3% at all 3 anatomical sites in the abaloparatide than placebo group at month 6 (18/122 [14.8%] vs 1/70 [1.4%], $P = .002$) and at month 12 (38/119 [31.9%] vs 1/66 [1.5%], $P < .0001$). At month 3, more men treated with abaloparatide than placebo had a >3% BMD increase at the LS (82/134 [61.2%] vs 21/68 [30.9%], $P < .0001$). A greater proportion of men treated with abaloparatide had an improvement in T-score category from osteoporosis to low BMD or normal when compared with placebo. In conclusion, use of abaloparatide compared with placebo for 12 mo resulted in significant and rapid improvements in BMD in men with osteoporosis from the ATOM study.

Keywords: abaloparatide, bone mineral density, fracture, osteoporosis in men, T-score

Lay Summary

Osteoporosis in men is an often-overlooked health problem. Although osteoporosis occurs more often in women, men with osteoporosis have a higher risk of complications and loss of life after breaking a bone. Abaloparatide is an injectable medication that helps build bone density. It is similar to a naturally occurring hormone known as parathyroid-related protein.

The Abaloparatide for the Treatment of Men with Osteoporosis (ATOM) study found that men treated with abaloparatide had increased bone density in the spine, hip, and thigh bone when compared to men given placebo. This study examined data from the ATOM trial and found that by the sixth month of treatment, significantly more men treated with abaloparatide had increased bone density of >3% at the spine, hip, and thigh bone than the men given placebo. An increase in spine bone density was seen as early as 3 mo in men treated with abaloparatide.

Also, after 12 mo of treatment, the category of patient T-score, based on bone density, improved from osteoporosis to low bone density or normal in a larger number of men treated with abaloparatide than those given placebo. Overall, abaloparatide treatment resulted in significant and rapid improvement in bone density in men.

Introduction

During their lifetime, approximately 1 in 4 men >50 yr of age will suffer an osteoporotic fracture.[1] The proportions of fracture-related morbidity and mortality events are higher in the male population, despite a lower prevalence of osteoporosis than in women.[2] Multiple factors, including puberty, sex hormones, levels of physical activity, and body size all lend to differences between men and women in bone development, impacting osteoporosis risk.[3] Fragility fractures in men account for approximately 30% of the substantial societal burden of osteoporosis, contributing to increasing health care costs and a decrease in patient quality of life.[3,4]

The risk of subsequent fracture is highest immediately after an initial fracture, highlighting the need for rapid and effective treatment in patients with a recent fracture.[5]

Abaloparatide is a synthetic, 34-amino acid peptide with homology to human parathyroid hormone-related protein (PTHrP), which favors bone formation by selectively activating PTH receptor type 1.[6-8] In the *A*baloparatide *C*omparator *T*rial *i*n *V*ertebral *E*ndpoints (ACTIVE, NCT01343004), abaloparatide significantly increased BMD in women with postmenopausal osteoporosis, and decreased risk of vertebral, nonvertebral, and clinical fractures when compared with placebo.[7] In a prospective, exploratory BMD responder analysis using data from the ACTIVE trial, a larger proportion of participants in the abaloparatide group experienced BMD increases at predetermined responder thresholds (>0%, >3%, and > 6%) at the LS, TH, and FN compared to placebo.[8]

In the 12-mo randomized, double-blind, placebo-controlled, phase 3 study, *A*baloparatide for the *T*reatment *o*f *M*en with Osteoporosis (ATOM, NCT03512262), men treated with abaloparatide had significant BMD improvements at the LS, TH, and FN when compared to placebo.[9] The most frequently reported adverse events (AEs) (≥5%) were injection site reaction, dizziness, nasopharyngitis, arthralgia, bronchitis, hypertension, and headache, and the proportion of patients experiencing an AE or serious AE was similar between treatment groups.[9] These findings are consistent with earlier studies in postmenopausal women.[7]

In this prespecified analysis of the ATOM study, the proportion of men who responded to treatment with abaloparatide at 3 responder thresholds (>0%, >3%, and > 6%) was evaluated.

Materials and Methods

Study Population

Men with primary or hypogonadism-associated osteoporosis were enrolled for 12 mo in the ATOM trial. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization, and applicable local regulations. The study documents were reviewed by central or, for some countries, local institutional review boards. Approval was obtained from all institutions, and written informed consent was obtained from all participants.

Detailed study design and eligibility criteria for ATOM have been previously described in Czerwinski et al.[9] Briefly, men 40 to 85 yr of age were randomized 2:1 to receive daily subcutaneous injections of abaloparatide 80 μg or matched placebo. Men with T-scores ≤ − 2.5 at the LS or hip (FN or TH), or ≤ −1.5 with a history of radiologic vertebral fracture or low trauma nonvertebral fracture in the past 5 yr were eligible. Men >65 yr of age with a T-score of ≤ − 2.0 were also eligible. T-scores were originally calculated using female BMD reference ranges. The protocol was later amended to change the BMD criteria to male reference ranges (as assessed by the central imaging vendor). Patients, previously ineligible based on female BMD reference data, were rescreened and randomized if they met the criteria based on male BMD reference data. Additionally, the study required participants to have a BMI of 18.5 to 33 kg/m^2, normal levels of calcium (albumin corrected), PTH, thyroid-stimulating hormone, phosphorus, and alkaline phosphatase.

All patients included in the study received daily calcium and vitamin D supplementation based on their need, as determined by the investigator, to ensure their daily intake remained in the range of 500 mg to 1000 mg and 400 to 800 IU, respectively, from pretreatment through the end of the treatment period.

Participants were excluded if they had experienced a severe vertebral fracture, >2 moderate vertebral fractures, or a fragility fracture within the past 12 mo. Additional exclusion criteria included treatment with PTH- or PTHrP-derived medications, bisphosphonates (IV anytime or oral within 3 yr of screening), or denosumab within the last 18 mo.

BMD Responder Analysis

The responder analysis was a prespecified endpoint of the ATOM study for exploratory purposes, and included participants from the intention-to-treat (ITT) population of ATOM who had LS and TH BMD measurements at baseline and month 12.

Prior studies have suggested that a 3% increase in BMD, based on DXA scanner precision of approximately 1% corresponding to the least significant change (LSC) in BMD at the 95% confidence limits of 3%, is a reasonable threshold for this type of responder analysis.[8,10-12] In the current study, participants were designated as responders if the treatment resulted in a BMD gain at or above the predetermined 3% LSC from baseline threshold at all 3 anatomic sites of measurement (LS, TH, and FN), as determined by centrally read DXA scan at the same visit (3, 6, or 12 mo), with the primary time point at 12 mo. BMD measurements were corrected for variations in DXA scanner calibrations, hardware upgrades, and cross-calibration measurements. Central adjudication of DXA scans occurred at BioClinica Medical Imaging in Princeton, NJ, USA.[9] Additionally, percent change in BMD from baseline of >0%, >3%, and > 6% was evaluated at each individual anatomical site with >0% representing any positive change, >3%, a recognized approximation of the LSC, and > 6%, signifying a more robust threshold of positive change.[7]

T-Score Analysis

T-score analysis was a prespecified exploratory endpoint of the ATOM study. T-scores (based upon the male reference database) were examined at baseline and month 12 of the study period to evaluate changes in disease state category in patients treated with abaloparatide compared with placebo. Based on LS and TH T-scores, disease state categories were defined as normal (both LS and TH T-scores ≥ − 1.0) or osteoporosis (either LS or TH T-score ≤ −2.5), and all other cases were defined as low bone mass (either LS or TH T-score > −2.5 and < −1.0, none of LS or TH T-scores ≤ − 2.5).

Statistical Analyses

The chi-square test was employed to compare the difference in the percentage of patients with percent change from baseline of >0%, >3%, and > 6% between the abaloparatide and placebo groups at each visit (3, 6, and 12 mo) at the LS, TH, and FN. Fisher's exact test was applied to any treatment group with less than 5 responders to calculate the *P* value.

The proportion of participants with a change in BMD T-score category from baseline to month 12 was analyzed using the Cochran–Mantel–Haenszel test stratified by baseline disease category (Table 1). No imputation of missing data was implemented.

Table 1. Demographics and clinical characteristics.[a]

Characteristics	Abaloparatide (n = 119)	Placebo (n = 66)	Overall (N = 185)
Age, mean (SD), years	68.1 (8.1)	67.7 (8.4)	68.0 (8.2)
Body mass index, mean (SD)	26.5 (3.5)	26.1 (3.5)	26.4 (3.5)
Race category, n (%)			
White	112 (94.1)	63 (95.5)	175 (94.6)
Asian	6 (5.0)	1 (1.5)	7 (3.8)
Black or African American	0	1 (1.5)	1 (0.5)
Native Hawaiian or other Pacific Islander	1 (0.8)	0	1 (0.5)
Other	0	1 (1.5)	1 (0.5)
Region, n (%)			
North America	56 (47.1)	36 (54.5)	92 (49.7)
Europe	63 (52.9)	30 (45.5)	93 (50.3)
25OHD, mean (SD), nmol/L	104.4 (46.4)	113.8 (47.1)	107.8 (46.8)
BMD T-score, mean (SD)			
LS	−2.1 (1.2)	−2.1 (1.1)	−2.1 (1.1)
TH	−1.6 (0.6)	−1.9 (0.7)	−1.7 (0.7)
FN	−2.1 (0.6)	−2.3 (0.6)	−2.2 (0.6)
BMD T-score category, n (%)			
LS			
≤−2.5	54 (45.4)	35 (53.0)	89 (48.1)
>−2.5	65 (54.6)	31 (47.0)	96 (51.9)
TH			
≤−2.5	9 (7.6)	12 (18.2)	21 (11.4)
>−2.5	110 (92.4)	54 (81.8)	164 (88.6)
FN			
≤−2.5	39 (32.8)	28 (42.4)	67 (36.2)
>−2.5	80 (67.2)	38 (57.6)	118 (63.8)
≥1 Prevalent vertebral fracture(s), n (%)	42 (35.3)	24 (36.4)	66 (35.7)
≥1 Prior fracture(s), n (%)	69 (58.0)	41 (62.1)	110 (59.5)
s-PINP, ng/mL			
Mean (SD)	49.2 (16.9)	46.2 (21.2)	48.1 (18.5)
Median (min, max)	47.3 (14.4, 106.2)	40.8 (19.2, 127.2)	45.5 (14.4, 127.2)
s-CTX, ng/mL			
Mean (SD)	0.350 (0.146)	0.322 (0.170)	0.340 (0.155)
Median (min, max)	0.324 (0.11, 0.81)	0.275 (0.11, 1.02)	0.304 (0.11, 1.02)

[a] Includes participants from the intention-to-treat population of ATOM, who had LS and TH BMD measurements at baseline and month 12. Abbreviations: s-CTX = serum carboxy-terminal cross-linking telopeptide of type I collagen; s-PINP, serum procollagen type I N-terminal propeptide

Results

Study Population

The ATOM study enrolled 228 men: 149 in the abaloparatide group and 79 in the placebo group, for whom patient demographics and characteristics have been previously described.[9] BMD data from the ATOM study ITT population for LS and TH at both baseline and month 12 were available for 185 participants—119 patients in the abaloparatide group and 66 patients in the placebo group. These patients were included in this analysis, and demographic and baseline characteristics for these patients are summarized in Table 1. At baseline, the proportion of men with T-scores ≤ − 2.5 at the LS, TH, and FN was 89/185 (48.1%), 21/185 (11.4%), and 67/185 (36.2%), respectively.

BMD Responder Analysis

Responders at all 3 anatomical sites (LS, TH, FN)

At 6 and 12 mo, a significantly greater proportion of men in the abaloparatide group had a > 3% BMD increase at all 3 anatomical sites compared with placebo (Figure 1 and Table 2). Specifically, at 6 mo, 18/122 (14.8%) men in the abaloparatide group compared with 1/70 (1.4%) in the placebo group (P = .002) and, at 12 mo, 38/119 (31.9%) men in the abaloparatide group compared with 1/66 (1.5%) in the placebo group (P < .0001) had a > 3% BMD increase at all 3 anatomical sites. Significantly more men in the abaloparatide group than in the placebo group also achieved a BMD increase of >6% at all 3 anatomical sites (11/119 [9.2%] vs 0; P = .0083) at month 12.

Response at the LS

At month 3, a significantly greater proportion of men treated with abaloparatide than placebo had a BMD increase of >3% at the LS (82/134 [61.2%] vs 21/68 [30.9%]; P < .0001) (Table 3). In addition, 35/134 men in the abaloparatide group compared with 4/68 in the placebo group (26.1% vs 5.9%, respectively) had a > 6% increase in BMD at the LS at 3 mo (P = .0005). Statistically significant responses of >3% and > 6% were sustained at months 6 and 12.

Response at the TH

At month 6, 34/122 (27.9%) men treated with abaloparatide compared with 5/70 (7.1%) treated with placebo met the >3% increase in BMD threshold at the TH (P = .0006) (Table 3). At month 12, 50/119 (42.0%) and 8/66 (12.1%) men treated with abaloparatide compared to placebo had a > 3% increase in BMD (P < .0001). A > 6% increase in TH BMD was seen in 15/119 (12.6%) participants treated with abaloparatide compared with 2/66 (3.0%) in the placebo group at month 12 (P = .0341).
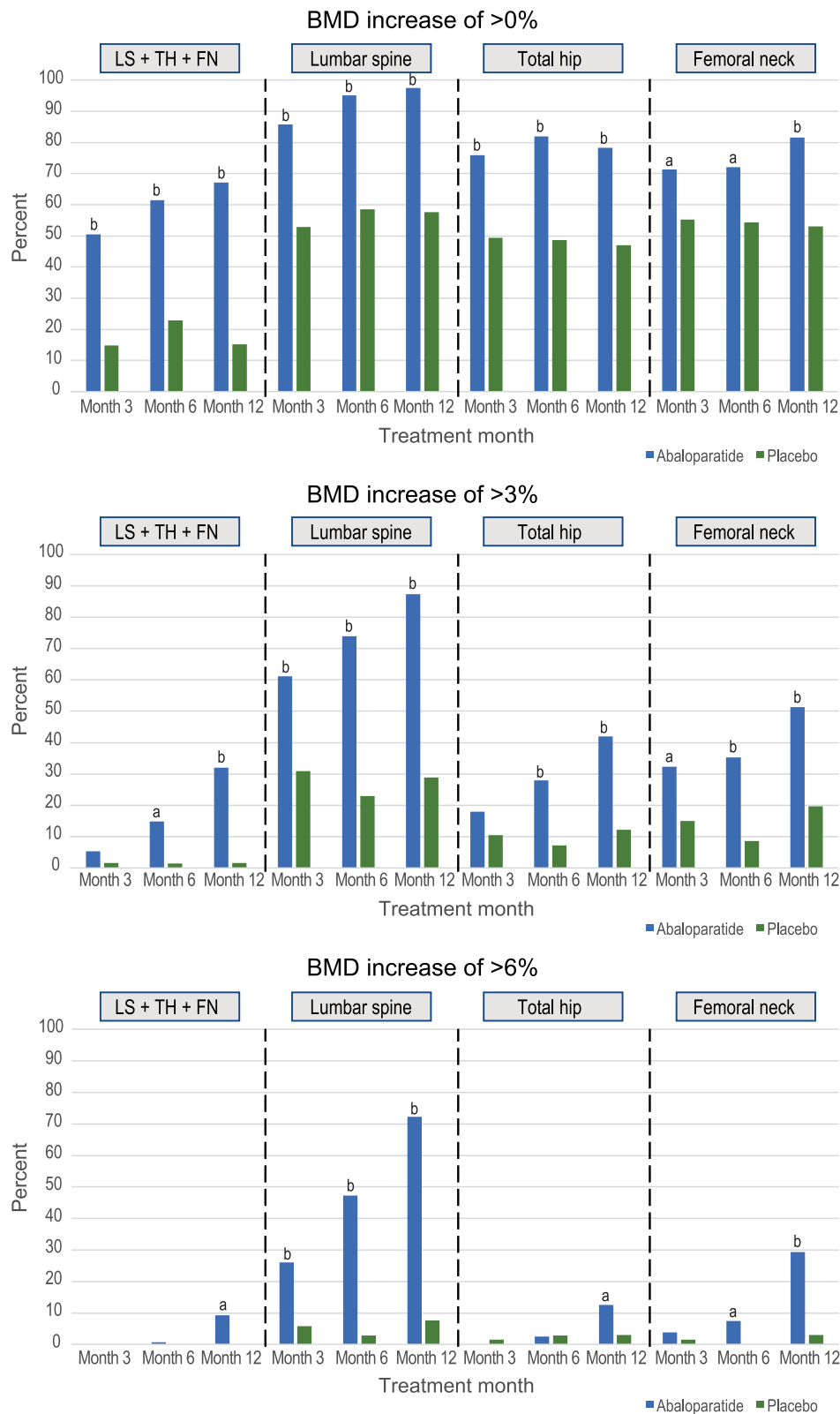
Figure 1. Proportion of men with BMD increase >0%, >3%, and > 6% at 3, 6, and 12 mo. [a] $P < .05$; [b] $P < .001$.

Response at the FN

At 3 mo, an FN BMD increase of >3% occurred in 43/133 (32.3%) men in the abaloparatide group compared with 10/67 (14.9%) in the placebo group ($P = .0085$) (Table 3). The difference between treatment groups remained statistically significant at months 6 and 12 ($P < .0001$). At month 6, 9/122 (7.4%) men in the abaloparatide group had a BMD increase of >6% compared with zero in the placebo group ($P = .0276$), with the difference between groups remaining significant at month 12 ($P < .0001$).

Table 2. BMD increase >3% at all 3 anatomical sites (LS, TH, and FN).

Assessment visit	Abaloparatide *n/N* (%)	Placebo *n/N* (%)	*P* value
Month 3	7/133 (5.3)	1/67 (1.5)	.2721
Month 6	18/122 (14.8)	1/70 (1.4)	.0020
Month 12	38/119 (31.9)	1/66 (1.5)	<.0001

n: number of participants with >3% increase in BMD at all anatomic sites (LS, TH, and FN). *N*: number of participants with a BMD assessment at all anatomic sites at the visit.

Table 3. BMD increase >3% at each individual anatomical site.

Anatomical location	Assessment visit, month	Abaloparatide *n/N* (%)	Placebo *n/N* (%)	*P* value
	3	82/134 (61.2)	21/68 (30.9)	<.0001
LS	6	91/123 (74.0)	16/70 (22.9)	<.0001
	12	104/119 (87.4)	19/66 (28.8)	<.0001
	3	24/133 (18.0)	7/67 (10.4)	.1611
TH	6	34/122 (27.9)	5/70 (7.1)	.0006
	12	50/119 (42.0)	8/66 (12.1)	<.0001
	3	43/133 (32.3)	10/67 (14.9)	.0085
FN	6	43/122 (35.2)	6/70 (8.6)	<.0001
	12	61/119 (51.3)	13/66 (19.7)	<.0001

n: number of participants >3% increase in BMD category at an individual anatomic site at the visit. *N*: number of participants with a BMD assessment for an individual anatomic site at the visit.

Table 4. Proportion of men with a baseline T-score category conversion.

Baseline T-score category	T-score category at end of treatment						*P* value
	Abaloparatide			Placebo			
	Normal *n/N* (%)	Low bone mass *n/N* (%)	Osteoporosis *n/N* (%)	Normal *n/N* (%)	Low bone mass *n/N* (%)	Osteoporosis *n/N* (%)	
Normal	4/4 (100)	0	0	3/3 (100)	0	0	<.0001
Low bone mass	6/68 (8.8)	62/68 (91.2)	0	2/25 (8.0)	20/25 (80.0)	3/25 (12.0)	
Osteoporosis	2/70 (2.9)	40/70 (57.1)	28/70 (40.0)	0	6/47 (12.8)	41/47 (87.2)	

n: number of participants who switched from baseline disease category to end of treatment disease category for corresponding row and column. *N*: number of participants who had a baseline evaluation at each category and also had an end of treatment BMD evaluation.

BMD T-score improvement

A T-score category change, based on LS and TH T-scores, from osteoporosis to low bone mass occurred in 40/70 (57.1%) and 6/47 (12.8%) men in the abaloparatide and placebo groups, respectively (Table 4). Improvement in T-score category from osteoporosis to normal occurred in 2/70 (2.9%) men in the abaloparatide group by the end of the study, compared with zero in the placebo group.

Most participants (62/68 [91.2%]) in the abaloparatide group with a baseline T-score in the low bone mass category did not have a change from their baseline category (Figure 2). There was a T-score shift to normal in 6/68 (8.8%) men with low bone mass at baseline treated with abaloparatide, similar to that for the placebo group 2/25 (8.0%). All of the low bone mass group receiving abaloparatide either maintained their baseline BMD category or improved to the normal BMD category, while 3/25 (12.0%) of patients receiving placebo in the low bone mass category declined to the osteoporosis category.

A total of 42/70 (60.0%) men in the abaloparatide group compared with 6/47 (12.8%) receiving placebo had a T-score category conversion from osteoporosis to low bone mass or normal. A significant proportion of men across all abnormal baseline T-score categories (osteoporosis and low bone mass) treated with abaloparatide resulted in an improvement in

T-score category by the end of treatment (*P* < .0001; Table 4, Figure 2).

Discussion

This prespecified responder analysis demonstrated that a larger proportion of men with osteoporosis treated with abaloparatide (18/122 [14.8%]) compared with placebo (1/70 [1.4%]) met the 3% LSC threshold at all anatomical sites (LS, TH, and FN) by 6 mo of treatment. At month 12, 38/119 (31.9%) men treated with abaloparatide and 1/66 (1.5%) men receiving placebo had a > 3% improvement in BMD at all anatomical sites. These results were consistent with a previous responder analysis performed in women treated with abaloparatide.[8] In Miller et al, a > 3% improvement in BMD at all 3 anatomical sites (LS, TH, and FN) occurred by month 6 in 116/609 (19.1%) and 6/650 (0.9%) of women receiving abaloparatide or placebo, respectively.[8] At month 12, 203/612 (33.2%) women in the abaloparatide group compared with 10/650 (1.5%) women in the placebo group had a > 3% improvement in BMD at all 3 anatomical sites (LS, TH, and FN).[8]

A significant proportion of men receiving abaloparatide had a > 3% improvement in BMD at the LS and FN as early as 3 mo into the study. In patients who have fractured,
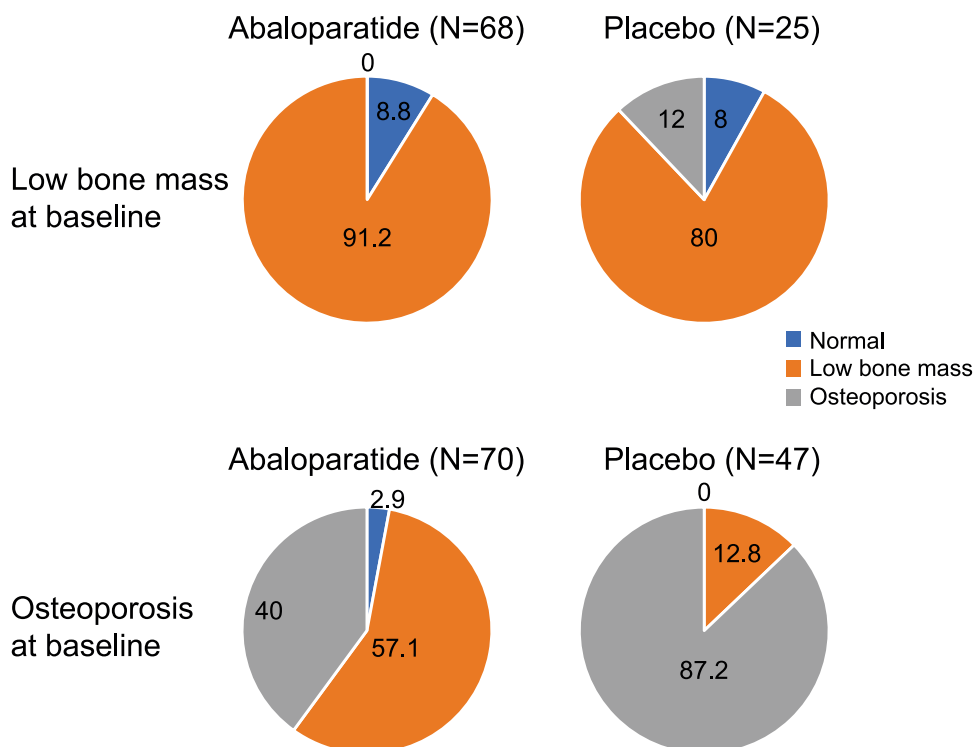
Abaloparatide (N=68)   Placebo (N=25)

Low bone mass at baseline

- Normal
- Low bone mass
- Osteoporosis

Abaloparatide (N=70)   Placebo (N=47)

Osteoporosis at baseline

Figure 2. Proportion of men with a T-score category shift from baseline to end of treatment.

an early response to osteoporosis treatment is important to minimize the risk of subsequent fracture, which is highest in the first 1–5 yr after an initial fracture, and near-term efficacy should be a consideration during treatment selection to help curtail imminent fracture risk.[5] Bone anabolic therapies (eg, PTH receptor agonists) have been demonstrated in multiple clinical trials to have superior BMD effects due to their ability to stimulate osteoblast bone formation.[11] Previously published data on abaloparatide in which multiple endpoints were analyzed have elucidated the mechanisms by which treatment with abaloparatide leads to increments in BMD.[7,9,11,13] The rapid BMD gains are indicative of rapid stimulation of osteoblasts by abaloparatide and an overall positive response indicative of a continuously positive coupling balance favoring bone formation through the selective binding of abaloparatide to the G protein–coupled conformation (RG) of the PTH-1 receptor.[6,7,9,11] The efficacy of PTH receptor agonists is related not only to the increase in BMD, but also to improved bone microarchitecture and strength.[13-17] This has been well documented in preclinical and clinical studies of abaloparatide.[14,15,18,19]

In this analysis, abaloparatide was associated with a greater proportion of men with improvement in T-score category from osteoporosis to low bone mass or normal than placebo. More men with osteoporosis at baseline (T-score LS or TH ≤ −2.5) transitioned to an improved T-score category than men categorized as having low bone mass at baseline. This is consistent with a prior study that showed that a greater proportion of participants transitioned to an improved T-score category when initial T-score was ≤ − 3.5, compared to those with higher initial T-scores.[20]

Responder analyses have been performed previously with antiresorptive and anabolic treatments for osteoporosis. In a 2-yr retrospective chart review of patients with osteoporosis who completed 18 to 24 mo of treatment with teriparatide, 83% and 40% of patients were responders (>3% increase in BMD) at the LS and FN, respectively.[21] This study had a small patient population ($N = 78$) that was predominantly women, did not provide results combining all 3 anatomical sites (LS, TH, and FN), and had a longer study period (2 yr) than the current study.[21]

In the ACTIVE trial, the BMD response rates were more robust in the women treated with abaloparatide compared with placebo at all time points (6, 12, and 18 mo) and all 3 sites and with teriparatide at all time points for TH and FN and at 6 and 12 mo for LS.[7] Though placebo is the only comparator group in the current study, the BMD response rates in the abaloparatide-treated men in ATOM appear similar to those observed in women treated with abaloparatide in the ACTIVE trial.[7,9] Although caution is warranted in making direct comparisons in response to other anabolic therapies across trials, these data suggest that the established clinical efficacy of different anabolic agents in women may be extrapolated to men. Furthermore, the increment in BMD in the ATOM population, as previously published in Czerwinski et al,[9] is consistent with the rapid rise in BMD reported in a study of romosozumab in men[22] and previous studies of anabolic treatments in men.[23,24]

An analysis of 4 separate randomized clinical trials involving sequential osteoporosis treatment in women, *A*ctive-cont*R*olled Fra*C*ture Study in Postmenopausal Women With Osteoporosis at *H*igh Risk (ARCH; NCT01631214 [romosozumab to alendronate]), *FRA*cture Study in Postmenopausal Wo*M*en With Ost*E*oporosis (FRAME; NCT01575834 [romosozumab to denosumab]), *ST*udy Evaluating the Effect of *R*omosoz*U*mab *C*ompared With *T*eriparatide in Postmenopa*U*sal Women With Osteoporosis at High Risk for Fracture P*R*eviously Treated With Bisphosphonat*E*

Therapy (STRUCTURE; NCT01796301 [alendronate to romosozumab], and a phase 2 extension study; NCT00896532 [denosumab to romosozumab]), evaluated individual sites (TH and LS) for BMD gains ≥3% and ≥ 6% with 1- and 2-yr data for ARCH, FRAME, and the phase 2 extension study, and 1-yr data for STRUCTURE.[25] By month 12 of the ARCH study, 1638/1722 (95.1%) and 1320/1781 (74.1%) patients achieved ≥3% BMD percent change from baseline at the LS and TH, respectively. Similar results were seen at the LS (3030/3151 [96.2%]) and TH (2485/3197 [77.7%]) in FRAME and the LS (179/197 [90.9%]) in STRUCTURE. Fewer patients achieved ≥3% BMD percentage change at the TH (92/197 [46.7%]) in STRUCTURE. Although 100% of patients achieved a ≥ 3% BMD percentage change in the LS from baseline by 24 mo in the phase 2 extension study, there were only 13 patients with evaluable data. BMD percentage change from baseline ≥3% at 12 mo occurred at the LS in 9/13 (69.2%) patients and at the TH in 1/13 (7.7%) patient. Limitations of this analysis included varied age and fracture prevalence within the patient populations. Also, baseline BMD had to be adjusted for each trial, except in the phase 2 extension trial due to a small patient population, in order to determine the change in BMD.

Of note, the studies mentioned above did not include a cumulative result of all anatomical sites (LS, TH, and FN). The heterogeneity in study design, population, and duration of treatment in the studies limits the comparative conclusions with the current responder analysis.

Study limitations

Study responses may not be generalizable to all populations, as the majority of study participants were white. The small participant sample and relatively short 12-mo duration of this study are also potential limitations of these analyses.[9] However, the proportion of responders at month 12 reported in the responder analysis in women using data from ACTIVE was similar to these results.[8] The proportion of women categorized as responders continued to increase through month 18, and a similar increase can be expected in men.[8] Although BMD change from baseline has been proposed as a surrogate for predicting fracture risk reduction,[26] additional studies are needed to establish the utility of percent change in BMD as a surrogate fracture risk marker. A goal of the Foundation for the National Institutes of Health (FNIH)-ASBMR Study to Advance BMD as a Regulatory Endpoint (SABRE) project is to identify a surrogate threshold effect (STE), which is the minimum threshold for a surrogate treatment effect that is a reliable predictor of a clinical outcome, to provide a framework for implementation of TH BMD as a surrogate endpoint in osteoporosis clinical trials.[27] The FNIH-ASBMR SABRE project validated change in TH BMD at 24 mo as a surrogate for fracture risk based on patient data from 61 415 participants in 16 randomized controlled trials that evaluated antiresorptive and anabolic osteoporosis treatments,[27] and the STE is within achievable BMD improvements with abaloparatide treatment.

Sex steroids affect the responsiveness of osteoblastic cells to PTH. In the ATOM study, men with clinical signs of hypogonadism or low testosterone at screening but who had not yet initiated treatment were excluded, and there were very few men with primary hypogonadism (6 patients [2.6%]) or secondary hypogonadism (1 patient [0.4%]) at screening.[9] Also, there were not prespecified subgroups of eugonadal and hypogonadal patients. Mean serum testosterone values at baseline were similar between groups and, when examining BMD change by total testosterone or estradiol level, there was no notable difference in BMD changes. Other clinical trials in men did not find a difference in treatment response between eugonadal and hypogonadal men.[24]

In conclusion, this analysis demonstrated that treatment with abaloparatide resulted in a greater proportion of men with osteoporosis having a > 3% increase in BMD at all 3 anatomical sites measured and improvement in T-score from their baseline category compared to placebo. Abaloparatide provided a rapid response rate, which is needed for patients with a very high or imminent fracture risk.

Author contributions

Ruban Dhaliwal (Investigation, Resources, Visualization, Writing—review & editing), David Kendler (Investigation, Writing—review & editing), Kenneth Saag (Investigation, Writing—review & editing), Steven Ing (Investigation, Writing—review & editing), Andrea Singer (Investigation, Writing—review & editing), Robert Adler (Investigation, Writing—review & editing), Leny Pearman (Writing—review & editing), Yamei Wang (Conceptualization, Data curation, Formal analysis, Writing—review & editing), and Bruce Mitlak (Conceptualization, Funding acquisition, Supervision, Writing—review & editing).

Conflicts of interest

R.D. serves on the scientific advisory board and/or as a consultant for Amgen, Alexion, Ultragenyx, and Radius, and received research grants (to the institution) from Alexion, Radius, Shire, and Takeda.

D.K. reports consultancies with Amgen, Eli Lilly, and Pfizer, honoraria for advice or public speaking from Amgen and Eli Lilly, and grants/research support from Radius and AstraZeneca.

K.S. reports research grants from Amgen, Mereo, and Radius, and consulting fees from Amgen and Daaichi Sankyo.

S.W.I. has received research grants paid to his institution from Alexion, Amgen, Amolyt, Calcilytix, Radius, Takeda, and Ultragenyx, and has served on an advisory board and/or consultant for Amgen, Bone Health & Osteoporosis Foundation, Extend Biosciences, Radius, and Soft Bones, Inc.

A.S. has received research grants paid to her institution from Radius and UCB, consulting fees from Agnovos, Amgen, Radius, and UCB, and speaking fees from Amgen and Radius.

R.A. has received research grants paid to his institution from Radius.

L.P., Y.W., and B.M. are employees of Radius.

Data availability

Data that underlie the results reported in a published article may be requested for further research 6 mo after the completion of FDA or EMA regulatory review of a marketing application (if applicable) or 18 mo after the trial completion (whichever is latest). Radius will review

requests individually to determine whether (i) the requests are legitimate and relevant and meet sound scientific research principles, and (ii) are within the scope of the participants' informed consent. Prior to making data available, requestors will be required to agree in writing to certain obligations, including without limitation, compliance with applicable privacy and other laws and regulations. Proposals should be directed to info@radiuspharm.com.

References

1. The Man's Guide to Osteoporosis. Mans-Guide-to-Osteoporosis-1.pdf (https://www.bonehealthandosteoporosis.org/wp-content/uploads/2016/02/Mans-Guide-to-Osteoporosis-1.pdf) Accessed November 10, 2022.

2. Curry SJ, Krist AH, Owens DK, et al. Screening for osteoporosis to prevent fractures: US preventive services task force recommendation statement. *JAMA*. 2018;319(24):2521–2531. https://doi.org/10.1001/jama.2018.7498.

3. Willson T, Nelson SD, Newbold J, Nelson RE, LaFleur J. The clinical epidemiology of male osteoporosis: a review of the recent literature. *Clin Epidemiol*. 2015;7:65–76. https://doi.org/10.2147/CLEP.S40966.

4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res*. 2007;22(3):465–475. https://doi.org/10.1359/jbmr.061113.

5. van Geel TA, Huntjens KM, van den Bergh JP, Dinant GJ, Geusens PP. Timing of subsequent fractures after an initial fracture. *Curr Osteoporos Rep*. 2010;8(3):118–122. https://doi.org/10.1007/s11914-010-0023-2.

6. Hattersley G, Dean T, Corbin BA, Bahar H, Gardella TJ. Binding selectivity of abaloparatide for PTH-type-1-receptor conformations and effects on downstream signaling. *Endocrinology*. 2016;157(1):141–149. https://doi.org/10.1210/en.2015-1726.

7. Miller PD, Hattersley G, Riis BJ, 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. https://doi.org/10.1001/jama.2016.11136.

8. 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. https://doi.org/10.1016/j.bone.2018.10.015.

9. Czerwinski E, Cardona J, Plebanski R, et al. the efficacy and safety of abaloparatide-SC in men with osteoporosis: a randomized clinical trial. *J Bone Miner Res*. 2022;37(12):2435–2442. https://doi.org/10.1002/jbmr.4719.

10. Hochberg MC, Ross PD, Black D, et al. Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Fracture Intervention Trial Research Group. *Arthritis Rheum*. 1999;42(6):1246–1254. https://doi.org/10.1002/1529-0131(199906)42:6<1246::AID-ANR22>3.0.CO;2-U.

11. 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. https://doi.org/10.1210/jc.2014-3718.

12. Miller PD, McClung MR, Macovei L, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res*. 2005;20(8):1315–1322. https://doi.org/10.1359/JBMR.050313.

13. Dempster DW, Zhou H, Rao SD, et al. Early effects of abaloparatide on bone formation and resorption indices in postmenopausal women with osteoporosis. *J Bone Miner Res*. 2021;36(4):644–653. https://doi.org/10.1002/jbmr.4243.

14. 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. https://doi.org/10.1007/s00198-017-4304-9.

15. 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. https://doi.org/10.1007/s00198-017-4323-6.

16. 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. https://doi.org/10.1016/j.bone.2016.11.027.

17. Varela A, Chouinard L, Lesage E, Smith SY, Hattersley G. 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. https://doi.org/10.1002/jbmr.3003.

18. 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. https://doi.org/10.1002/jbm4.10346.

19. Cosman F, Hans D, Shevroja E, Wang Y, Mitlak B. Effect of abaloparatide on bone microarchitecture assessed by trabecular bone score in women with osteoporosis: post hoc analysis of ACTIVE and ACTIVExtend. *J Bone Miner Res*. 2023;38(4):464–470. https://doi.org/10.1002/jbmr.4764.

20. Berry SD, Dufour AB, Travison TG, et al. Changes in bone mineral density (BMD): a longitudinal study of osteoporosis patients in the real-world setting. *Arch Osteoporos*. 2018;13(1):124. https://doi.org/10.1007/s11657-018-0528-3.

21. Kim SY, Zhang M, Bockman R. Bone mineral density response from teriparatide in patients with osteoporosis. *HSS J*. 2017;13(2):171–177. https://doi.org/10.1007/s11420-016-9537-1.

22. Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab*. 2018;103(9):3183–3193. https://doi.org/10.1210/jc.2017-02163.

23. Kurland ES, Cosman F, McMahon DJ, Rosen CJ, Lindsay R, Bilezikian JP. Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab*. 2000;85(9):3069–3076. https://doi.org/10.1210/jc.85.9.3069.

24. Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res*. 2003;18(1):9–17. https://doi.org/10.1359/jbmr.2003.18.1.9.

25. Cosman F, Kendler DL, Langdahl BL, et al. Romosozumab and antiresorptive treatment: the importance of treatment sequence. *Osteoporos Int*. 2022;33(6):1243–1256. https://doi.org/10.1007/s00198-021-06174-0.

26. Black DM, Bauer DC, Vittinghoff E, et al. Treatment-related changes in bone mineral density as a surrogate biomarker for fracture risk reduction: meta-regression analyses of individual patient data from multiple randomised controlled trials. *Lancet Diabetes Endocrinol*. 2020;8(8):672–682. https://doi.org/10.1016/S2213-8587(20)30159-5.

27. Eastell R, Vittinghoff E, Lui LY, et al. Validation of the surrogate threshold effect for change in bone mineral density as a surrogate endpoint for fracture outcomes: the FNIH-ASBMR SABRE Project. *J Bone Miner Res*. 2022;37(1):29–35. https://doi.org/10.1002/jbmr.4433.