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Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis
A Randomized Clinical Trial

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IMPORTANCE Additional therapies are needed for prevention of osteoporotic fractures. Abaloparatide is a selective activator of the parathyroid hormone type 1 receptor.

OBJECTIVE To determine the efficacy and safety of abaloparatide, 80 µg, vs placebo for prevention of new vertebral fracture in postmenopausal women at risk of osteoporotic fracture.

DESIGN, SETTING, AND PARTICIPANTS The Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) was a phase 3, double-blind, RCT (March 2011-October 2014) at 28 sites in 10 countries. Postmenopausal women with bone mineral density (BMD) T score ≤−2.5 and >−5.0 at the lumbar spine or femoral neck and radiological evidence ≥2 mild or ≥1 moderate lumbar or thoracic vertebral fracture or history of low-trauma nonvertebral fracture within the past 5 years were eligible. Postmenopausal women (>65 y) with fracture criteria and a T score ≤−2.0 and >−5.0 or without fracture criteria and a T score ≤−3.0 and >−5.0 could enroll.

INTERVENTIONS Blinded, daily subcutaneous injections of placebo (n = 821); abaloparatide, 80 µg (n = 824); or open-label teriparatide, 20 µg (n = 818) for 18 months.

MAIN OUTCOMES AND MEASURES Primary end point was percentage of participants with new vertebral fracture in the abaloparatide vs placebo groups. Sample size was set to detect a 4% difference (57% risk reduction) between treatment groups. Secondary end points included change in BMD at total hip, femoral neck, and lumbar spine in abaloparatide-treated vs placebo participants and time to first incident nonvertebral fracture. Hypercalcemia was a prespecified safety end point in abaloparatide-treated vs teriparatide participants.

RESULTS Among 2463 women (mean age, 69 years [range, 49-86]), 1901 completed the study. New morphometric vertebral fractures occurred less frequently in the active treatment groups vs placebo. The Kaplan-Meier estimated event rate for nonvertebral fracture was lower with abaloparatide vs placebo. BMD increases were greater with abaloparatide than placebo (all $P < .001$). Incidence of hypercalcemia was lower with abaloparatide (3.4%) vs teriparatide (6.4%) (risk difference [RD], −2.96 [95% CI, −5.12 to −0.87]; $P = .006$).

	Participants With Fracture, No. (%)			Abaloparatide vs Placebo		
	Abaloparatide (n = 824)	Placebo (n = 821)	Teriparatide (n = 818)	Risk Difference (95% CI)	RR or HR (95% CI)	*P* Value
New vertebral fracture	4 (0.6)	30 (4.2)	6 (0.8)	−3.64 (−5.42 to −2.10)	RR, 0.14 (0.05 to 0.39)	<.001
Nonvertebral fracture	18 (2.7)	33 (4.7)	24 (3.3)	−2.01 (−4.02 to −0.00)	HR, 0.57 (0.32 to 1.00)	.049

CONCLUSIONS AND RELEVANCE Among postmenopausal women with osteoporosis, the use of subcutaneous abaloparatide, compared with placebo, reduced the risk of new vertebral and nonvertebral fractures over 18 months. Further research is needed to understand the clinical importance of RD, the risks and benefits of abaloparatide treatment, and the efficacy of abaloparatide vs other osteoporosis treatments.

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Osteoporosis is associated with substantial social, economic, and public health burdens. Based on 2010 US Census data, Wright et al[1] estimated the prevalence of osteoporosis among women aged 50 to 69 years at 3.4 million. Another 18.8 million US women in that age group were estimated to have low bone mass at the femoral neck or lumbar spine. Additionally, Cawthon et al[2] have estimated that the lifetime risk of osteoporotic fracture for a 60-year-old woman is 44%. Fractures are associated with decreased quality of life,[3] including reduced independence,[4] and osteoporotic fractures[5,6] are associated with increased morbidity and mortality.[7]

Experiencing a major osteoporotic fracture increases the risk of subsequent fractures,[8,9] and risk is highest in the first few years after the fracture.[10-12] Osteoanabolic therapy is often recommended for women at risk of future fracture, including those with recent fracture or with multiple fractures,[13] but evidence of rapid fracture protection is lacking.[14]

Abaloparatide is a peptide that selectively binds to the RG conformation of the parathyroid hormone type 1 receptor.[15] As a result of its mechanism of action, it was hypothesized that abaloparatide would have a more pronounced anabolic action on bone compared with teriparatide.

The primary objective of this study was to determine the efficacy and adverse events of subcutaneous abaloparatide use compared with placebo for prevention of new vertebral fracture in postmenopausal women with osteoporosis.

Key Points

Question Is abaloparatide effective compared with placebo and teriparatide when used as a treatment to reduce the risk of new vertebral and nonvertebral fractures?

Findings This double-blind randomized clinical trial including 2463 postmenopausal women with osteoporosis showed that abaloparatide was associated with significantly greater reduction in incidence of new vertebral fractures and nonvertebral fractures compared with placebo. Hypercalcemia was less frequent with abaloparatide than with teriparatide.

Meaning Abaloparatide may represent a meaningful treatment option for postmenopausal women who have osteoporosis but requires testing against other osteoporosis treatments.

Methods

Study Design

The Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) was an international, randomized, placebo- and active-controlled trial including postmenopausal women with osteoporosis. Women were randomized 1:1:1 to receive daily subcutaneous injections of abaloparatide, 80 µg, or matching placebo,or teriparatide, 20 µg. Abaloparatide and matching placebo were administered using a double-blind format, while teriparatide, because it could be administered only via its trademarked injection pen, was given open label. The treatment period was 18 months.

Study Participants

Postmenopausal women aged 49 to 86 years were eligible if they had bone mineral density (BMD) by dual energy x-ray absorptiometry T score of less than or equal to −2.5 and greater than −5.0 at the lumbar spine or femoral neck together with radiologic evidence of at least 2 mild vertebral fractures or at least 1 moderate vertebral fracture[16] or history of a low-trauma fracture of the forearm, humerus, sacrum, pelvis, hip, femur, or tibia within the past 5 years. Women older than 65 years who met fracture criteria but had a T score of less than or equal to −2.0 and greater than −5.0 were eligible. Women older than 65 years were eligible without fracture criteria if either BMD T score was less than or equal to −3.0 and greater than −5.0. Eligibility required normal serum values for calcium, intact parathyroid hormone, phosphorus, and alkaline phosphatase and a 25-hydroxyvitamin D level of greater than 15 ng/mL (37.5 nmol/L [SI conversion, multiply by 2.496]). Women were excluded if they had more than 4 mild, moderate, or any severe vertebral fractures (consistent with definitions described by Genant et al[16]), fewer than 2 evaluable lumbar vertebrae, or if hip BMD was unevaluable. Participants were ineligible if they had evidence of metabolic bone disease or malabsorption or were taking any medications that would interfere with bone metabolism. Women were also excluded if they used bisphosphonates for more than 3 months in the past 5 years or denosumab within the past year. Women with a history of osteosarcoma were also excluded. (See the ACTIVE Trial Protocol in Supplement 1 for full inclusion and exclusion criteria.)

Participants provided written informed consent, and the protocol was approved by the respective institutional review boards.

Randomization and Blinding

Between April 26, 2011, and March 11, 2013, participants were randomized using a permuted-blocks design with a block size of 6 in a ratio of 1:1:1 to 1 of the 3 treatment groups. Randomized distribution of participants to study groups was double-blind. Abaloparatide and placebo were administered with identical pen injector devices under identical storage and dispensing conditions. Because the teriparatide device is a trademarked pen, it could not be reproduced, and the drug is not approved for dispensing from a different injection device (eg, a syringe) to blind it. After opening the identical assigned study medication kit after randomization on day 1, it became apparent to investigators and patients whether open-label teriparatide or either double-blind abaloparatide or double-blind placebo had been assigned.

Efficacy End Points

The primary efficacy end point of this study was the percentage of participants with 1 or more incidents of new morphometric vertebral fracture. Anteroposterior and lateral radiographs of the lumbar and thoracic spine were obtained at baseline and at the end of treatment. Radiologists (Bioclinica-Synarc) graded each woman's vertebrae according to the semiquantitative technique of Genant et al[16] which

defines a decrease in height of 20% to 25% as mild, 26% to 40% as moderate, and more than 40% as severe. Treatment was blinded from radiologists. A second radiologist reviewed radiographs in which an incident fracture had been identified to confirm the reading; if necessary, a third radiologist adjudicated the incident fracture. All treatments were blinded from adjudicators.

Nonvertebral fractures (a secondary end point) were fractures that excluded those of the spine, sternum, patella, toes, fingers, skull, and face and those with high trauma, defined as a fall from a height equal to or higher than the level of a stool, chair, or the first rung of a ladder. These nonvertebral fractures were initially self-reported but required verification from source documents. Treatments were blinded from all assessors.

Changes in BMD from baseline were assessed at total hip, femoral neck, and lumbar spine at months 6, 12, and 18 (Bioclinica-Synarc). 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) were measured at months 1, 3, 6, 12, and 18 (Nordic Biosciences) in a subset of participants.

Per the study's statistical analysis plan (Supplement 2), preplanned exploratory end points included assessment of clinical fractures (all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine), major osteoporotic fractures (fractures of the upper arm, wrist, hip, or clinical spine), and analyses comparing abaloparatide and teriparatide.

Safety

Safety evaluations included physical examinations, assessment of vital signs, clinical laboratory tests, and reporting of adverse events at each study visit. Twelve-lead electrocardiograms were performed at screening and at each study visit prior to and 1 hour after injection of study drug. Serum calcium concentrations were assessed at preinjection and at 4 hours postinjection on day 1, at months 1, 3, 6, 9, and 12, and in the morning only at the month 18 visit. The protocol allowed discontinuation of calcium, vitamin D, and the study drug for hypercalcemia or hypercalciuria, which caused 1 participant from the abaloparatide group and 1 patient from the teriparatide group to discontinue study participation.

The protocol specified that participants be withdrawn from the study if they had confirmed significant deterioration from baseline (>7.0%) of BMD at lumbar spine or hip; experienced treatment-related serious adverse events; developed severe hypersensitivity to subcutaneous abaloparatide or teriparatide; were unable to complete study treatment; refused treatment; developed protocol-defined hypercalcemia or hypercalciuria; or were lost to follow-up. Adverse events and serious adverse events were coded according to the *Medical Dictionary for Regulatory Activities 17.1*.

Study Oversight

This study was conducted in compliance with Good Clinical Practice and the ethical principles stated in the Declaration of Helsinki. Several measures were prespecified to assure participant safety. Participants were not enrolled unless they completed an extensive informed consent evaluation. All participants were provided calcium and vitamin D and were required to meet a minimal vitamin D level for enrollment. Participants with confirmed bone loss from baseline of greater than 7.0% at the lumbar spine, total hip, or femoral neck were discontinued from the study. Participants who experienced a fracture while in the study were offered an option to discontinue and receive alternative treatment. All participants in the subcutaneous abaloparatide and placebo groups were offered, after 18 months of treatment, enrollment in an extension study in which they were treated with alendronate for 24 months. Study protocols were approved by appropriate health authorities and ethics committees at each site. An independent data and safety monitoring board monitored study safety (see eAppendix 2 in Supplement 3 for a listing of members).

Statistical Analysis

A statistical analysis plan (available in Supplement 2) was created prior to data finalization and unblinding. There were 3 populations for efficacy analyses. The intent-to-treat (ITT) population, which included all participants who were randomized into the study and received a study medication kit on day 1, was the primary population used for all efficacy analyses except for those of vertebral fracture. The modified ITT population, which included all ITT participants who had both pretreatment and postbaseline spine x-rays, was the primary population used for analyses of vertebral fracture only. The per-protocol population, which included modified ITT participants who adhered with treatment and had no protocol violations, was used as a supportive population for efficacy analyses; findings for the per-protocol population, which were consistent with the ITT analyses, are not included in this report.

The primary efficacy end point of this study was the percentage of participants with 1 or more incidents of new morphometric vertebral fracture comparing abaloparatide and placebo. Key secondary end points included percent change in BMD at the total hip, femoral neck, and lumbar spine at 18 months and incident nonvertebral fractures, both of which were compared between abaloparatide and placebo. Additional comparisons are also described in this section. To control the overall significance level, a sequential testing plan (with 8 specific tests after the primary comparison) was defined. A hierarchical approach[17] controlled the overall type I error rate at the 2-sided significance level of 5% by prespecifying the order of the hypothesis tests in a fixed sequence before performing the tests. The efficacy end points were tested in the following sequence: new vertebral fracture (abaloparatide vs placebo); BMD at the total hip, femoral neck, lumbar spine (abaloparatide vs placebo at 18 months); nonvertebral fracture (abaloparatide vs placebo); BMD at the total hip and femoral neck (abaloparatide vs teriparatide at 6 months); nonvertebral fracture (abaloparatide vs teriparatide); and BMD at lumbar spine (abaloparatide vs teriparatide at 6 months). Each of the tests was performed sequentially at the 2-sided significance level of 5% to claim statistical significance. At any step, if the significance level of 5% was not attained, the *P* values for the subsequent comparisons were

generated as nominal for exploratory purposes. All statistical analyses other than the fixed sequential testing were prespecified exploratory analyses, including analyses of clinical fractures and major osteoporotic fractures, which are described in this report.

The number of women with at least 1 new vertebral fracture was compared using the Fisher exact test (between abaloparatide and placebo groups in the modified ITT population). To evaluate the statistical effect of missing data on incidence of new vertebral fractures, a sensitivity analysis was performed based on the multiple imputation method. This method used a logistic regression model to augment the data set by imputing the missing outcome multiple times to characterize the uncertainty of the imputation. The covariates in the logistic model are listed in the statistical analysis plan (Supplement 2). The primary efficacy analysis was repeated using each of the augmented data sets, and the results were combined according to Rubin.[18] Results of the sensitivity analysis were similar to the primary efficacy analysis.

Time to nonvertebral fracture was compared using the log-rank test in all participants through the whole observational period of 19 months (18 months of treatment plus 1 month of follow-up). The Cox proportional hazards model was used to calculate hazard ratios (HRs). Formal statistical tests were performed in abaloparatide vs placebo groups and abaloparatide vs teriparatide groups as specified in the sequential testing plan.

This study reports percent change in BMD from baseline at each study visit, which was compared using a mixed-effect repeated-measure model. An analysis of covariance model with missing data imputed and based on the last observation carried forward is reported in eFigure 1 (in Supplement 3).

Bone turnover marker levels, reported as a log ratio of post-baseline divided by baseline, were compared among groups using a mixed-effect repeated-measure model on a randomly selected subset of approximately 200 participants in each treatment group with paired measurements at baseline and follow-up. Treatment differences in log values were transformed into geometric mean ratios for treatment comparisons (eFigure 2 in Supplement 3). Median percent change from baseline in bone turnover marker levels was graphically displayed among treatment groups. Hypercalcemia, defined as albumin-corrected serum calcium of at least 10.7 mg/dL (≥2.67 mmol/L) at any time point, was a prespecified safety end point and was analyzed using a χ^2 test.

The sample size was determined to provide 90% power at a 2-sided α of .05 to detect a difference of 4% between treatments, assuming a vertebral fracture rate of 7% in participants receiving placebo and 3% in participants receiving abaloparatide, a difference of 4%, equivalent to 57% risk reduction. The sample size was calculated using a large-scale binomial approximation. The required sample size was 622 per group. To ensure an analysis size of 622 women, an overall sample size of approximately 800 per treatment group was recruited, anticipating that approximately 20% of participants might not have a second set of evaluable radiographs available for analysis. This sample size would provide more than 90% power to detect significant percentage changes, consistent with other drugs, in total hip, femoral neck, and lumbar spine BMD. It would provide similar power to detect differences in hypercalcemia incidence between the abaloparatide and teriparatide groups.

All statistical analyses were performed using SAS version 9.4.

Results

A total of 5268 women underwent screening for the trial. There were 2032 who failed to meet eligibility criteria, 698 declined participation, 53 were not randomized, and 22 were excluded for other reasons (**Figure 1**).

A total of 2463 women were randomized at 28 study centers in 10 countries to receive abaloparatide (n = 824 [33.5%]), placebo (n = 821 [33.3%]), or open-label teriparatide (n = 818 [33.2%]). Overall, 1901 participants (77.2%) completed all study visits: 637 (77.6%) in the placebo group, 606 (73.5%) in the abaloparatide group, and 658 (80.4%) in the teriparatide group, and 2118 (86%) participants had postrandomization radiographs that were assessed for new morphometric vertebral fractures (primary end point).

At baseline, mean age was 68.8 years, and mean femoral neck T score was −2.1. Approximately 24% of participants had a prevalent vertebral fracture, 31% reported a history of nonvertebral fracture within the past 5 years, and 37% had no prior fractures (**Table 1**). Baseline characteristics were similar among treatment groups. During the study, the mean daily dosages of vitamin D were 613 IU in the placebo group, 723 IU in the abaloparatide group, and 625 IU in the teriparatide group, and mean daily calcium dosages were 986 mg in the placebo group, 955 mg in the abaloparatide group, and 894 mg in the teriparatide group.

Each participant recorded study drug administration and local tolerance in a weekly diary. According to the duration of each individual's exposure during this study treatment period (when participants were to remain on study medication), mean percent adherence to study drug administration was greater than 90% for each of the 3 treatment groups.

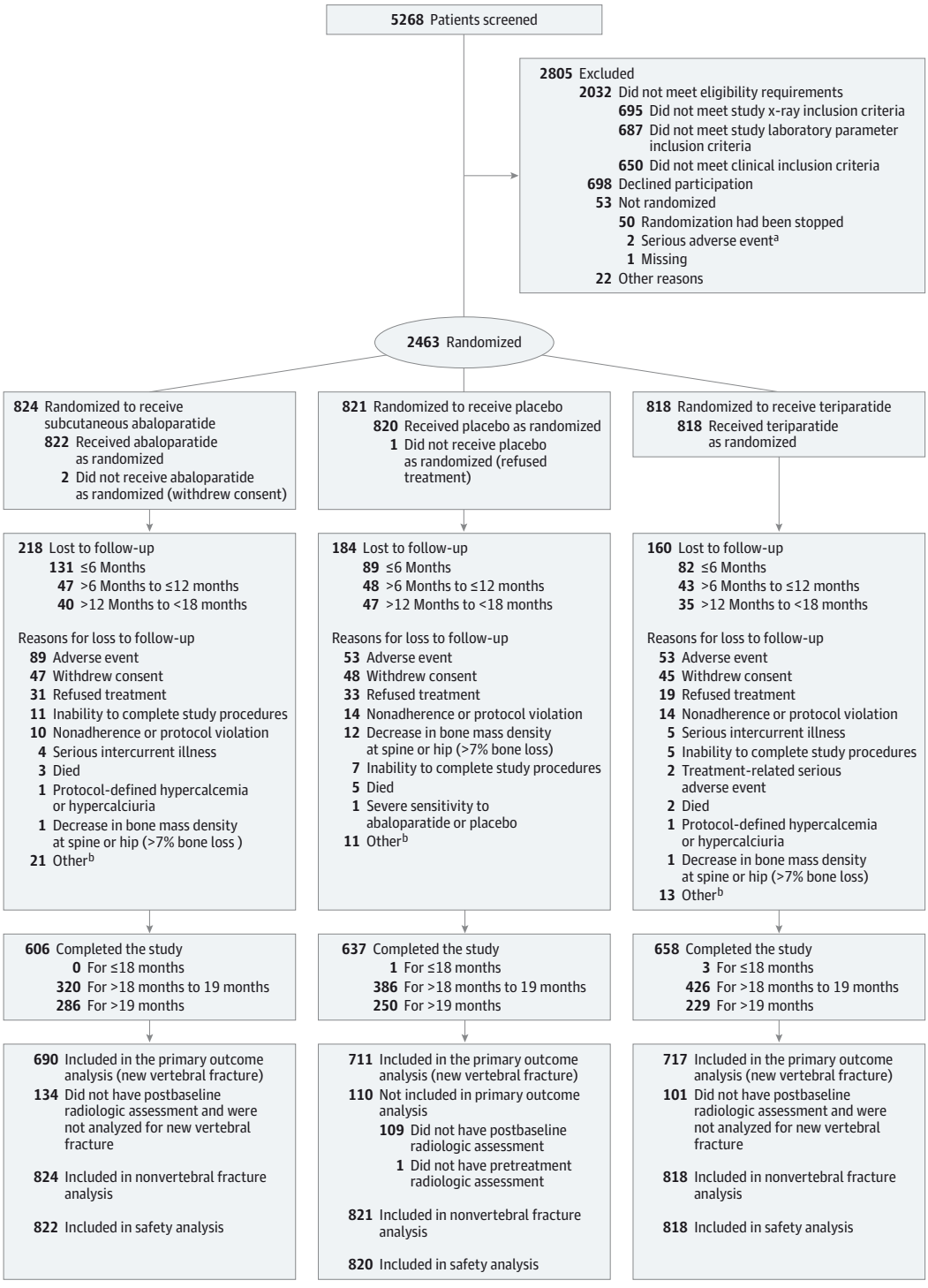
Primary Outcome

New morphometric vertebral fractures occurred in 0.58% (n = 4) of participants in the abaloparatide group and in 4.22% (n = 30) of those in the placebo group (risk difference [RD] vs placebo, −3.64 [95% CI, −5.42 to −2.10]; relative risk, 0.14 [95% CI, 0.05 to 0.39]; $P < .001$; **Table 2**). In the teriparatide group, new morphometric vertebral fractures occurred in 0.84% (n = 6) of participants (RD vs placebo, −3.38 [95% CI, −5.18 to −1.80]; relative risk, 0.20 [95% CI, 0.08 to 0.47]; $P < .001$). Results of the sensitivity analysis were similar to results of the primary efficacy analysis.

Secondary Outcomes

Secondary outcomes for this study are reported in hierarchical order as defined by the statistical analysis plan (in Supplement 2). Compared with placebo at 18 months, the abaloparatide-treated group demonstrated significant changes from baseline BMD at the total hip (4.18% vs −0.10%; treatment difference, 4.25% [95% CI, 3.90% to 4.59%]), femoral

Figure 1. Patient Flow Through Phases of a Randomized Trial of Abaloparatide vs Placebo for New Vertebral Fracture Prevention Among Postmenopausal Women With Osteoporosis



[a] Two women experienced events that resulted in hospitalization and were therefore categorized as having serious adverse events (1, fracture of the left femoral neck; 1, head of the humerus fracture); however, these events occurred prior to and, in fact, prevented randomization. They were not associated with study treatment.

[b] Category includes patients lost to follow-up for the following reasons: did not return, refused to perform procedures, no longer wished to participate, administrative reasons, unknown reasons, and breast cancer (1 patient).

Table 1. Mean Baseline Demographics and Clinical Characteristics

Variable	Abaloparatide (n = 824)	Placebo (n = 821)	Teriparatide (n = 818)
Age, mean (SD), y	68.9 (6.5)	68.7 (6.5)	68.8 (6.6)
Time since menopause, mean (SD), y	20.6 (8.3)	19.9 (8.1)	20.4 (8.2)
Weight, mean (SD), kg	61.1 (10.0)	61.2 (10.2)	61.2 (10.3)
Body mass index, mean (SD)[a]	25.0 (3.5)	25.1 (3.6)	25.2 (3.6)
Race, No. (%)			
White	663 (80.5)	655 (79.8)	645 (78.9)
Asian	128 (15.5)	131 (16.0)	137 (16.7)
Black or African American	26 (3.2)	23 (2.8)	24 (2.9)
Other	7 (0.8)	12 (1.5)	12 (1.5)
T score, mean (SD)			
Femoral neck	−2.2 (0.6)	−2.2 (0.7)	−2.1 (0.7)
Total hip	−1.9 (0.7)	−1.9 (0.8)	−1.9 (0.8)
Lumbar spine	−2.9 (0.9)	−2.9 (0.8)	−2.9 (0.9)
Bone mass density , mean (SD), g/cm^2			
Femoral neck	0.730 (0.091)	0.732 (0.099)	0.737 (0.096)
Total hip	0.766 (0.090)	0.767 (0.098)	0.773 (0.094)
Lumbar spine	0.829 (0.109)	0.823 (0.100)	0.831 (0.108)
≥1 Prevalent vertebral fracture(s), No. (%)	177 (21.5)	188 (22.9)	220 (26.9)
≥1 Prior nonvertebral fracture(s), No. (%)[b]	248 (30.1)	266 (32.4)	240 (29.3)
No history of prior fracture, No. (%)	305 (37.0)	307 (37.4)	308 (37.7)

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Assessed within the last 5 years based on fractures that occurred prior to visit 3 (day 1 of study). Excludes fractures of the spine, sternum, patella, toes, fingers, skull, and facial bones.

Table 2. Fracture Efficacy End Points After 18 Months of Treatment

	Study Participants With Fracture, No. (%)[a]			Abaloparatide vs Placebo			Abaloparatide vs Teriparatide			Teriparatide vs Placebo		
	Abaloparatide (n = 824)	Placebo (n = 821)	Teriparatide (n = 818)	RD (95% CI)[b]	HR (95% CI)[c]	*P* Value[d]	RD (95% CI[b])	HR (95% CI)[c]	*P* Value[d]	RD (95% CI)[b]	HR (95% CI)[c]	*P* Value[d]
Primary End Point												
New vertebral fracture	4 (0.6)	30 (4.2)	6 (0.8)	−3.64 (−5.42 to −2.10)	RR, 0.14 (0.05 to 0.39)[e]	<.001				−3.38 (−5.18 to −1.80)	RR, 0.20 (0.08 to 0.47)[e]	<.001
Secondary End Point												
Nonvertebral fracture	18 (2.7)	33 (4.7)	24 (3.3)	−2.01 (−4.02 to −0.00)	0.57 (0.32 to 1.00)	.049	−0.55 (−2.34 to 1.24)	0.79 (0.43 to 1.45)	.44	−1.46 (−3.50 to 0.58)	0.72 (0.42 to 1.22)	.22
Exploratory End Points												
Major osteoporotic fracture	10 (1.5)	34 (6.2)	23 (3.1)	−4.73 (−8.07 to −1.40)	0.30 (0.15 to 0.61)	<.001	−1.65 (−3.18 to −0.11)	0.45 (0.21 to 0.95)	.03	−3.09 (−6.53 to 0.36)	0.67 (0.39 to 1.14)	.14
Clinical fracture	27 (4.0)	49 (8.3)	35 (4.8)	−4.24 (−7.93 to −0.54)	0.57 (0.35 to 0.91)	.02	−0.73 (−2.89 to 1.43)	0.81 (0.49 to 1.33)	.40	−3.51 (−7.22 to 0.21)	0.71 (0.46 to 1.09)	.11

Abbreviations: HR, hazard ratio; RD, risk difference.

[a] The percentage of new vertebral fractures was calculated using the modified intent-to-treat population at 18 months (placebo, n = 711; abaloparatide, n = 690; teriparatide, n = 717). The percentage of nonvertebral, major osteoporotic, and clinical fractures was cumulative Kaplan-Meier estimates using the intent-to-treat population at 19 months (the entire observational period including 18 months of treatment plus 1 month of follow-up).

[b] The 95% CI for RD for new vertebral fractures was calculated using the Newcombe method[19]; 95% CIs for RDs for nonvertebral, major osteoporotic, and clinical fractures were calculated using the normal approximation with difference in Kaplan-Meier estimates and standard error by Greenwood.[20]

[c] Values are reported as HR (95% CI) unless otherwise indicated.

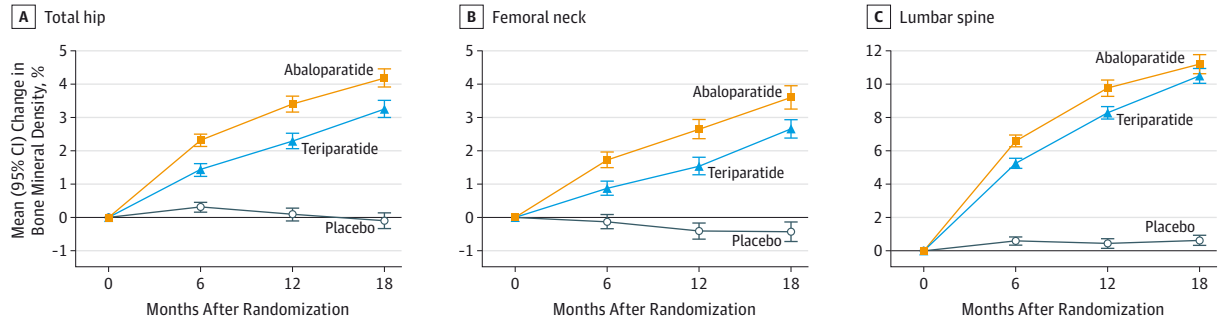
[d] *P* values for new vertebral fractures were derived using the Fisher exact test. *P* values for nonvertebral, major osteoporotic, and clinical fractures were calculated using the log-rank test.

[e] Values comparing abaloparatide vs placebo, abaloparatide vs teriparatide, and teriparatide vs placebo are reported as relative risks (95% CIs) for new vertebral fractures.

neck (3.60% vs −0.43%; treatment difference, 4.01% [95% CI, 3.58% to 4.45%]), and lumbar spine (11.20% vs 0.63%; treatment difference, 10.37% [95% CI, 9.75% to 10.98%]), all comparisons of abaloparatide with placebo, $P < .001$ (**Figure 2**). Analysis with the last observation carried forward was also performed and is presented in eFigure 1 (in Supplement 3).

The Kaplan-Meier estimated event rate for nonvertebral fracture was 2.7% in the abaloparatide group vs 4.7% in the placebo group, representing an RD of −2.01 (95% CI, −4.02 to −0.00; hazard ratio [HR], 0.57 [95% CI, 0.32 to 1.00]; $P = .049$). The test of the proportional hazards assumption was not significant ($P = .76$). However, the log-log plot

Figure 2. Change From Baseline in Bone Mineral Density



No. of participants evaluated

Abaloparatide	822	736	651	615	822	736	651	615	823	738	652	617
Placebo	820	762	693	651	820	762	693	651	821	764	694	650
Teriparatide	818	754	705	660	818	754	705	660	818	755	704	665

Mean percent changes in bone mineral density at the total hip, femoral neck, and lumbar spine were evaluated using dual-energy x-ray absorptiometry based on the intent-to-treat population. Values shown are mean percent change from baseline using a mixed-effect repeated-measures model. Improvements in bone mineral density associated with abaloparatide were significantly greater than with placebo at all 3 sites and at all time points ($P < .001$). Improvements with teriparatide were significantly greater than with placebo at all 3 sites at all time points ($P < .001$). Improvements with abaloparatide were significantly greater than those with teriparatide at the total hip and femoral neck at all time points ($P < .001$) and at lumbar spine at 6 and 12 months ($P < .001$). Error bars indicate 95% CIs.

showed slight deviations from the assumption, suggesting that the log-rank test was more robust than the Wald-based inference using the Cox proportional hazards model when making statistical inferences. There were 2 hip fractures over the course of the study; both hip fractures were in the placebo group (eTable in Supplement 3).

BMD increases from baseline to month 6 in the abaloparatide-treated group were greater than those in the teriparatide group at the total hip (2.32% vs 1.44%; treatment difference, 0.83% [95% CI, 0.58% to 1.08%]; $P < .001$) and femoral neck (1.72% vs 0.87%; treatment difference, 0.81% [95% CI, 0.49% to 1.12%]; $P < .001$; Figure 2). The last observation carried forward showed similar results (eFigure 1 in Supplement 3).

The Kaplan-Meier estimated event rate for nonvertebral fracture was 2.7% in the abaloparatide group vs 3.3% in the teriparatide group, indicating an RD of −0.55 (95% CI, −2.34 to 1.24; HR, 0.79 [95% CI, 0.43 to 1.45]; $P = .44$; **Figure 3**, Table 2).

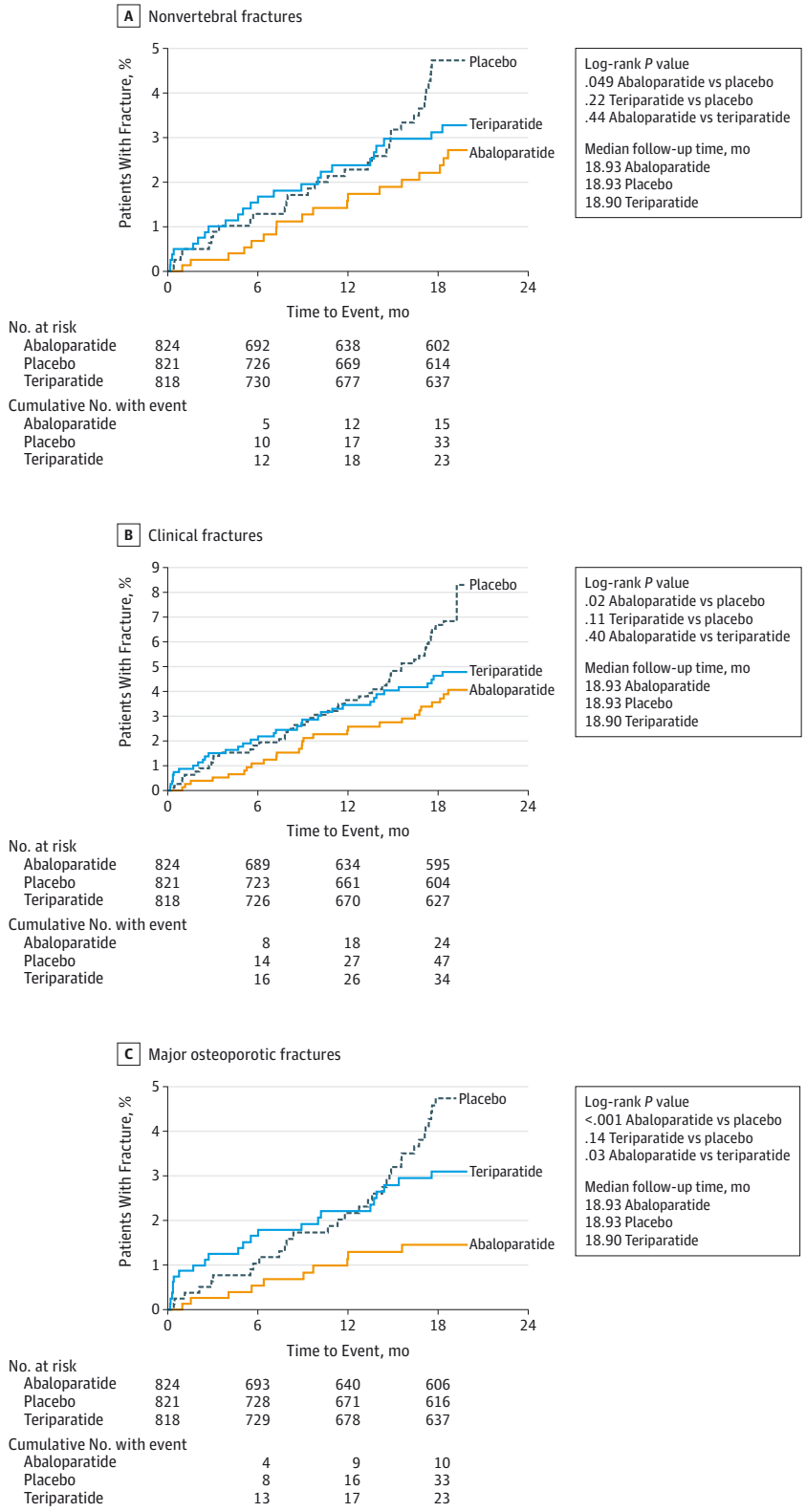
Because of the hierarchical sequence, comparison of change in BMD at the lumbar spine at 6 months between abaloparatide and teriparatide must be interpreted as exploratory. There was a significantly greater increase in the abaloparatide-treated group (6.58%) than in the teriparatide group (5.25%) (treatment difference, 1.32 [95% CI, 0.86 to 1.79]; nominal $P < .001$; Figure 2). The last observation carried forward showed similar results (eFigure 1 in Supplement 3).

Prespecified Exploratory Outcomes

There was a significant reduction with abaloparatide vs placebo in 2 prespecified exploratory fracture end points. For all clinical fractures, regardless of level of trauma, the Kaplan-Meier estimated event rate was 4.0% for the abaloparatide group vs 8.3% for the placebo group (RD, −4.24 [95% CI, −7.93 to −0.54]; HR, 0.57 [95% CI, 0.35 to 0.91]; $P = .02$; Table 2). For major osteoporotic fractures, the Kaplan-Meier estimated event rate was 1.5% for the abaloparatide group vs 6.2% for the placebo group (RD, −4.73 [95% CI, −8.07 to −1.40]; HR, 0.30 [95% CI, 0.15 to 0.61]; $P < .001$; Table 2). Comparison of abaloparatide with teriparatide for major osteoporotic fractures was also a prespecified exploratory end point. The Kaplan-Meier estimated event rate for teriparatide was 3.1% (RD for abaloparatide vs teriparatide, −1.65 [95% CI, −3.18 to −0.11]; HR, 0.45 [95% CI, 0.21 to 0.95]; $P = .03$; Table 2). Kaplan-Meier curves for time to clinical fracture and major osteoporotic fracture are shown in Figure 3. Kaplan-Meier estimated event rates in the teriparatide group of 3.3% for nonvertebral fractures (RD vs placebo, −1.46 [95% CI, −3.50 to 0.58]; HR, 0.72 [95% CI, 0.42 to 1.22]; $P = .22$; Table 2), 4.8% for clinical fractures (RD vs placebo, −3.51 [95% CI, −7.22 to 0.21]; HR, 0.71 [95% CI, 0.46 to 1.09]; $P = .11$; Table 2), and 3.1% for major osteoporotic fractures (RD vs placebo, −3.09 [95% CI, −6.53 to 0.36]; HR, 0.67 [95% CI, 0.39 to 1.14]; $P = .14$; Table 2) were not significantly different from placebo (Figure 3).

Prespecified exploratory BMD outcomes included comparison between abaloparatide and placebo for change from baseline at 6 and 12 months at total hip, femoral neck, and lumbar spine (Figure 2). For total hip at 6 months, BMD increased 2.32% (95% CI, 2.13% to 2.50%) in the abaloparatide group vs 0.31% (95% CI, 0.16% to 0.47%) in the placebo group ($P < .001$), and at 12 months, BMD increased 3.41% (95% CI, 3.17%% to 3.64%) in the abaloparatide group vs 0.09% (95% CI, −0.10% to 0.29%) in the placebo group ($P < .001$). For femoral neck at 6 months, BMD increased 1.72% (95% CI, 1.49% to 1.95%) in the abaloparatide group vs −0.13% (95% CI, −0.34% to 0.08%) in the placebo group ($P < .001$), and at 12 months, BMD increased 2.65% (95% CI, 2.36% to 2.93%) in the abaloparatide group vs −0.41% (95% CI, −0.64% to −0.17%) in the placebo group ($P < .001$). For lumbar spine at 6 months, BMD increased 6.58% (95% CI,

Figure 3. Time to Event of Nonvertebral, Clinical, and Major Osteoporotic Fractures



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 vs placebo, the hazard ratio (HR) was 0.57 (95% CI, 0.32-1.00; $P = .049$) and for teriparatide vs placebo, the HR was 0.72 (95% CI, 0.42-1.22; $P = .22$).

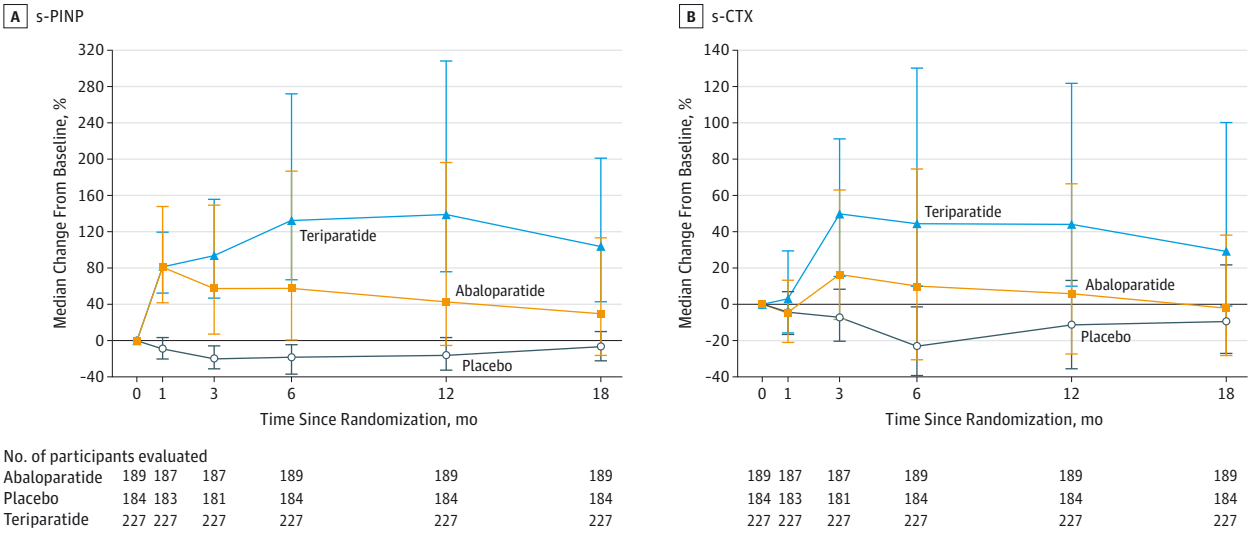
B, Curves indicate time to the first clinical fracture—a prespecified exploratory end point. Clinical fractures were defined as all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine. For abaloparatide vs placebo, the HR was 0.57 (95% CI, 0.35-0.91; $P = .02$) and for teriparatide vs 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 vs placebo, the HR was 0.30 (95% CI, 0.15-0.61; $P < .001$) and for teriparatide vs placebo, the HR was 0.67 (95% CI, 0.39-1.14; $P = .14$).

The median durations in days of follow-up for all 3 fracture categories were 568 (interquartile range [IQR], 557-572) for placebo, 568 (IQR, 477-572) for abaloparatide, and 567 (IQR, 558-571) for teriparatide.

6.22% to 6.95%) in the abaloparatide group vs 0.60% (95% CI, 0.35% to 0.84%) in the placebo group ($P < .001$), and at 12 months, BMD increased 9.77% (95% CI, 9.28% to 10.25%) in the abaloparatide group vs 0.45% (95% CI, 0.17% to 0.72%) in the placebo group ($P < .001$). The last observation carried forward showed similar results (eFigure 1 in Supplement 3).

Figure 4. Median Change From Baseline in Serum Bone Metabolism Markers Over Time by Treatment Group



No. of participants evaluated

Abaloparatide	189	187	187	189	189	189
Placebo	184	183	181	184	184	184
Teriparatide	227	227	227	227	227	227

Abaloparatide	189	187	187	189	189	189
Placebo	184	183	181	184	184	184
Teriparatide	227	227	227	227	227	227

Error bars indicate median interquartile ranges. Levels indicate change from baseline for a bone turnover marker population subset (n = 184 placebo, n = 189 abaloparatide, and n = 227 teriparatide participants).

A, All comparisons for serum procollagen type I N-terminal propeptide (s-PINP) of abaloparatide vs placebo and of teriparatide vs placebo, $P < .001$. For abaloparatide vs teriparatide at 1 month, $P = .13$; at month 3, $P = .02$; at months 6, 12, and 18, $P < .001$.

B, Comparisons for serum carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) of abaloparatide vs placebo at 1 month, $P = .40$; at 3, 6, and 12 months, $P < .001$; at 18 months, $P = .27$. For teriparatide vs placebo, $P < .01$ at all time points. For abaloparatide vs teriparatide, $P < .001$ at all time points except for at 1 month, $P = .04$.

Change from baseline BMD for the teriparatide group is shown in Figure 2. For the total hip, teriparatide was associated with a BMD increase of 2.29% (95% CI, 2.07% to 2.52%) at 12 months and an increase of 3.26% (95% CI, 3.00% to 3.51%) at 18 months (Figure 2). For the femoral neck, teriparatide was associated with a BMD increase of 1.54% (95% CI, 1.28% to 1.80%) at 12 months and an increase of 2.66% (95% CI, 2.38% to 2.93%) at 18 months (Figure 2). For the lumbar spine, teriparatide was associated with a BMD increase of 8.28% (95% CI, 7.90% to 8.66%) at 12 months and an increase of 10.49% (95% CI, 10.05% to 10.94%) at 18 months (Figure 2). Improvements with abaloparatide were significantly greater than those with teriparatide at the total hip and femoral neck at all time points ($P < .001$), at lumbar spine at 6 and 12 months ($P < .001$), but not at lumbar spine at 18 months ($P = .17$). The last observation carried forward showed similar results (eFigure 1 in Supplement 3).

Other Efficacy Outcomes

The bone formation marker s-PINP and the resorption marker s-CTX showed significant increases among abaloparatide- and teriparatide-treated participants compared with placebo at 3, 6, and 12 months ($P < .001$; **Figure 4**; eFigure 2 in Supplement 3). There was a different pattern of change in bone turnover markers with the 2 anabolic agents. For bone formation, initial increases in the first month were similar, but by 3 months, bone formation began to decrease in the abaloparatide group compared with the teriparatide group. Similarly, the increase in s-CTX was less in the abaloparatide group than in the teriparatide group.

Adverse Events

Adverse events were evaluated descriptively. There were no evident differences between treatment groups in proportion of participants with 1 or more treatment-emergent adverse events, serious adverse events, or adverse events leading to death. Serious treatment-emergent adverse events appeared balanced between treatment groups: placebo, 90 (11.0%); abaloparatide, 80 (9.7%); and teriparatide, 82 (10.0%).

There were more adverse events leading to study discontinuation in the abaloparatide group (9.9%) than in either the teriparatide (6.8%) or placebo (6.1%) groups. Adverse events that most often led to study drug discontinuation in the abaloparatide group were nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%), which were generally mild to moderate in severity. Serious adverse events leading to discontinuation appeared to occur at similar rates in the abaloparatide and teriparatide groups and with apparently greater frequency than in the placebo group (**Table 3**).

Hypercalcemia was predefined as albumin-corrected serum calcium level of at least 10.7 mg/dL (or ≥2.67 mmol/L), and overall incidence was significantly lower in the abaloparatide group (3.4%) than the teriparatide group (6.4%) (RD, −2.96 [95% CI, −5.12 to −0.87]; $P = .006$) for any time point including predose and postdose. Likewise, the 4-hour, postdose overall incidence of hypercalcemia was significantly lower in the abaloparatide group (3.42%) than the teriparatide group (6.1%) ($P = .01$). There was no evidence of increased cardiovascular risk associated with hypercalcemia in participants receiving abaloparatide.

Table 3. Safety and Adverse Events[a]

	Abaloparatide (n = 822)	Placebo (n = 820	Teriparatide (n = 818)
All treatment-emergent adverse events	735 (89.4)	718 (87.6)	727 (88.9)
Serious treatment-emergent adverse events	80 (9.7)	90 (11.0)	82 (10.0)
Deaths[b]	3 (0.4)	5 (0.6)	3 (0.4)
Adverse events leading to discontinuation	81 (9.9)	50 (6.1)	56 (6.8)
Discontinuation due to >7.0% BMD decrease[c]	1/218 (0.5)	12/184 (6.5)	1/160 (0.6)
Most frequently observed adverse events[d]			
Hypercalciuria	93 (11.3)	74 (9.0)	102 (12.5)
Dizziness	82 (10.0)	50 (6.1)	60 (7.3)
Arthralgia	71 (8.6)	80 (9.8)	70 (8.6)
Back pain	70 (8.5)	82 (10.0)	59 (7.2)
Nausea	68 (8.3)	25 (3.0)	42 (5.1)
Upper respiratory tract infection	68 (8.3)	63 (7.7)	73 (8.9)
Headache	62 (7.5)	49 (6.0)	51 (6.2)
Hypertension	59 (7.2)	54 (6.6)	41 (5.0)
Influenza	52 (6.3)	39 (4.8)	34 (4.2)
Nasopharyngitis	48 (5.8)	66 (8.0)	53 (6.5)
Urinary tract infection	43 (5.2)	38 (4.6)	41 (5.0)
Palpitations	42 (5.1)	3 (0.4)	13 (1.6)
Pain in extremity	40 (4.9)	49 (6.0)	42 (5.1)
Constipation	37 (4.5)	42 (5.1)	34 (4.2)
Hypercalcemia (prespecified safety end point)[e]	28/820 (3.4)[f]	3/817 (0.4)	52/816 (6.4)
Adverse events of special interest[g]			
Orthostatic hypotension[h]	140 (17.1)	134 (16.4)	127 (15.5)
Neoplasms, benign, malignant, and unspecified[i]	20 (2.4)	29 (3.5)	31 (3.8)
Fall[j]	4 (0.5)	2 (0.2)	4 (0.5)
Drug hypersensitivity[j,k]	2 (0.2)	2 (0.2)	0
Renal impairment[j]	2 (0.2)	4 (0.5)	3 (0.4)
Myocardial infarction[j]	1 (0.1)	2 (0.2)	2 (0.2)

[a] Values are reported as No. (%) unless otherwise indicated. Statistical testing of adverse events was not prespecified in the statistical analysis plan (Supplement 2), with the exception of hypercalcemia.

[b] Causes of death in the placebo group: bowel cancer, intestinal obstruction, myocardial infarction, dissecting aneurysm of the aorta, sudden death. Causes of death in the abaloparatide group: sepsis, bronchiectasis, ischemic heart disease. Causes of death in the teriparatide group: pancreatic cancer, general health deterioration, cardiorespiratory arrest.

[c] The denominator indicates the total number of patients who discontinued study participation.

[d] Indicates adverse events that occurred in at least 5% of patients in any single study group.

[e] Hypercalcemia defined as albumin-corrected serum calcium of at least 10.7 mg/dL (≥2.67 mmol/L) at any time point, which was a prespecified safety end point and was analyzed using the χ^2 test. Values are reported as No. with hypercalcemia/No. in study group (%).

[f] For abaloparatide and teriparatide vs placebo, $P < .001$; for abaloparatide vs teriparatide, $P = .006$.

[g] Adverse events of special interest were selected based on those related to mechanism of action, drug class effects and/or ongoing review of the study.

[h] Derived from vital sign data as a decrease in systolic blood pressure of at least 20 mm Hg from a supine position to standing or of at least 10 mm Hg in diastolic blood pressure from a supine position to standing in a postdose measurement.

[i] Summarized by system organ class.

[j] Based on patient self-report and assessed by the investigator.

[k] None of the events of drug hypersensitivity were associated with the study drug but were allergic reactions to other drugs provided to the participant.

Discussion

In this trial of postmenopausal women with osteoporosis, daily subcutaneous administration of abaloparatide for 18 months significantly reduced the risk of new vertebral and nonvertebral fractures compared with placebo. Treatment with abaloparatide was also associated with modestly higher BMD gains, especially at sites rich in cortical bone, compared with the placebo and teriparatide groups. The incidence of hypercalcemia was lower with abaloparatide than with teriparatide treatment, consistent with proportionally less bone resorption with abaloparatide. Overall, there were no differences in serious adverse events between the treatment groups.

Comparison of abaloparatide vs teriparatide for the primary efficacy end point was not part of the study objectives because the study would have required a sample size of approximately 22 000 per treatment group to provide 90% power to detect the treatment difference between abaloparatide (observed rate, 0.58%) and teriparatide (observed rate, 0.84%) based on our study results. Teriparatide treatment was associated with reduction in new vertebral fractures. In contrast to the findings of Neer et al,[14] the incidence of nonvertebral

fractures in the teriparatide-treated group was not significantly different from placebo in this study. However, the current trial enrolled a larger and broader population than the teriparatide fracture trial, and this trial did not require a prevalent vertebral fracture for enrollment. These factors may contribute to the different findings in these studies.

Changes in bone turnover markers with abaloparatide vs teriparatide treatment are consistent with changes in BMD with abaloparatide. The similar early increase in s-PINP and the less prominent increase in s-CTX with abaloparatide compared with teriparatide support the hypothesis that abaloparatide might have an enhanced net anabolic effect compared with teriparatide.[21,22] Despite being lower in the abaloparatide group vs the teriparatide group, bone formation, as measured by s-PINP, still remained 50% above baseline in the abaloparatide group at 18 months. Although the effect of increases in formation vs resorption on BMD and bone strength is not understood, it is possible that the smaller increases in formation, coupled with a lesser increase in markers of bone resorption, are consistent with larger early increases in BMD and earlier fracture protection. Further research is needed to clarify the effects of differing patterns of bone turnover markers to better understand the interplay of formation and resorption.

Differences in the effects of teriparatide and abaloparatide may be related to differing biologic effects. The differential binding of abaloparatide compared with teriparatide leads to parathyroid type 1 receptor conformation binding selectivity that favors anabolic activity.[15,23,24] As a result, abaloparatide may provide more transient stimulation of osteoblast cyclic adenosine monophosphate production and may result in lower expression of osteoblast-derived RANK-ligand. This could result in less stimulation of bone resorption.

Early antifracture efficacy has been highlighted as a major need in osteoporosis, particularly among patients with prior fractures.[25,26] In the current trial, the Kaplan-Meier curves for time to first event for nonvertebral fractures suggest early fracture risk reduction. Similar findings were made for the prespecified exploratory end points of major osteoporotic fractures and clinical fractures with abaloparatide treatment.

To ensure the safety of participants in a placebo-controlled trial, the following safeguards, including an informed consent that clearly defined risks, were incorporated into the trial design. Adequate intake of calcium and vitamin D, which are recognized treatments for reducing fracture risk, was required during the trial for all participants.[27-29] There were strict limitations on the range of acceptable BMD and number and type of fractures prior to study entry to limit the overall risk. The trial was also overseen by an external independent data monitoring committee that periodically reviewed unblinded safety data. Each participant who sustained a radiologically confirmed incident fracture was required to sign an additional informed consent if the participant chose to remain in the study. BMD was measured every 6 months, and if excessive bone loss[30] was identified and confirmed in any participant, study medication was discontinued and the participant was offered conventional treatment. In addition, at the end of the 18-month study, any participants randomized to receive the placebo were offered active open-label treatment with alendronate for 2 additional years.

Study Limitations

This study has limitations. Sixty-three percent of participants had a prior fracture; it cannot be determined from these data whether abaloparatide would have similar preventive and osteoanabolic effects among participants at lower risk for fracture. In this study, only a small number of fracture events occurred across treatment groups, with the event rate in the placebo group being smaller than anticipated. Although the event rate was lower than anticipated in the sample size calculation, the reduction in risk was larger than anticipated. These data indicate a reduction of risk until 18 months of treatment; it is not clear how long the benefit associated with abaloparatide may endure. In addition, the open-label teriparatide group may have resulted in bias in reporting subjective measures, such as safety events or differences in adherence, because participants and investigators were aware of the treatment.

Conclusions

Among postmenopausal women with osteoporosis, the use of subcutaneous abaloparatide, compared with placebo, reduced the risk of new vertebral and nonvertebral fractures over 18 months. Further research is needed to understand the clinical importance of RD, the the risks and benefits of abaloparatide treatment, and the efficacy of abaloparatide vs other osteoporosis treatments.

ARTICLE INFORMATION

Author Contributions: Dr Miller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hattersley, Williams.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Miller, Hattersley, Williams, Hu, Harris, Fitzpatrick, Cosman.
Critical revision of the manuscript for important intellectual content: Miller, Hattersley, Riis, Williams, Lau, Russo, Alexandersen, Zerbini, Hu, Fitzpatrick, Cosman, Christiansen.
Statistical analysis: Lau, Russo, Hu.
Administrative, technical, or material support: Hattersley, Riis, Williams, Fitzpatrick.
Study supervision: Miller, Hattersley, Williams, Russo, Zerbini, Harris.

Conflict of Interest Disclosures: Drs Fitzpatrick, Harris, Hattersley, Hu, and Williams, are employees of Radius Health, the sponsor of the study. Drs Alexandersen, Lau, and Russo are employees of the Center for Clinical and Basic Research, which was contracted by the study sponsor to collect participant data. Drs Christiansen and Riis are employees of Nordic Bioscience, which was contracted by the study sponsor to recruit participants, manage study participants, review all data, and manage data analyses. Dr Cosman reports serving as an advisor to Amgen, Eli Lilly, Merck, and Radius Health; serving as a consultant to Amgen, Eli Lilly, and Radius Health; and having received medication and funding for investigator-initiated studies from Amgen and Eli Lilly. Dr Miller reports being a member of scientific advisory boards for AgNovos, Amgen, Eli Lilly, Merck, Radius Health, Roche, and Ultragenyx; receiving research grants from Alexion, Amgen, Boehringer-Ingelheim, Daiichi-Sankyo, Eli Lilly, Immunodiagnostics, Merck, Merck Serono, National Bone Health Alliance, Novartis, Radius Health, Regeneron, Roche Diagnostics, and Ultragenyx; and serving on data safety committees for Allergan, and the Grünenthal Group. Dr Zerbini reports serving on advisory

boards for Eli Lilly, Pfizer, and Sanofi and receiving grants for research from Amgen, Eli Lilly, Merck, Novartis, Pfizer, Radius Health, and Sanofi.

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