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Odanacatib, a Cathepsin-K Inhibitor for Osteoporosis: A Two-Year Study in Postmenopausal Women With Low Bone Density

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ABSTRACT

Cathepsin K, a cysteine protease expressed in osteoclasts, degrades type 1 collagen. Odanacatib selectively and reversibly inhibited cathepsin K and rapidly decreased bone resorption in preclinical and phase I studies. A 1-year dose-finding trial with a 1-year extension on the same treatment assignment was performed in postmenopausal women with low bone mineral density (BMD) to evaluate the safety and efficacy of weekly doses of placebo or 3, 10, 25, or 50 mg of odanacatib on BMD and biomarkers of skeletal remodeling. Women with BMD *T*-scores of −2.0 or less but not less than −3.5 at the lumbar spine or femoral sites were randomly assigned to receive placebo or one of four doses of odanacatib; all received vitamin D with calcium supplementation as needed. The primary endpoint was percentage change from baseline lumbar spine BMD. Other endpoints included percentage change in BMD at hip and forearm sites, as well as changes in biomarkers of skeletal remodeling. Twenty-four months of treatment produced progressive dose-related increases in BMD. With the 50-mg dose of odanacatib, lumbar spine and total-hip BMD increased 5.5% and 3.2%, respectively, whereas BMD at these sites was essentially unchanged with placebo (−0.2% and −0.9%). Biochemical markers of bone turnover exhibited dose-related changes. The safety and tolerability of odanacatib generally were similar to those of placebo, with no dose-related trends in any adverse experiences. In summary, 2 years of weekly odanacatib treatment was generally well-tolerated and increased lumbar spine and total-hip BMD in a dose-related manner in postmenopausal women with low BMD. © 2010 American Society for Bone and Mineral Research.

KEY WORDS: BONE MINERAL DENSITY; CATHEPSIN K; CLINICAL TRIAL; ODANACATIB; OSTEOPOROSIS; PHASE 2B; POSTMENOPAUSAL WOMEN

Introduction

Osteoporosis results from an imbalance between bone resorption and bone formation favoring bone resorption. Low bone mineral density (BMD) and accompanying micro-architectural deterioration result in increased skeletal fragility and an increased risk of fracture.

The most commonly used drugs for the treatment of osteoporosis inhibit osteoclast-mediated bone resorption. Osteoclasts are hematopoietically derived multinucleated giant cells that resorb bone by focal attachment and demineralization, followed by the enzymatic degradation of organic bone matrix. The demineralization is achieved by the secretion of acid onto the bone surface. The organic matrix (mainly type 1 collagen, the principal bone matrix protein) is degraded primarily by the enzymatic action of cysteine proteases, particularly cathepsin K (CatK). CatK is the most abundantly expressed cysteine protease in osteoclasts and exhibits collagenolytic activity under acidic conditions. CatK, expressed primarily in osteoclasts, is an attractive target for selective inhibition to reduce bone resorption.[1–3]

Although no CatK inhibitor is currently marketed for osteoporosis treatment or prevention, studies of three CatK inhibitors for the treatment of osteoporosis have been reported: balicatib,[4–6] relacatib,[7] and odanacatib (ODN).[8] Balicatib is highly selective for CatK in enzyme assays but has lesser

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selectivity in living cells.[9] In vitro studies have shown that a basic moiety in its chemical structure results in its accumulation in the acidic environment of the lysosomes at concentrations sufficient to inhibit cathepsins B and L and possibly others.[9,10] Clinical studies of balicatib demonstrated BMD increases in postmenopausal women, but treatment was associated with cutaneous adverse experiences.[6] Relacatib is a potent but nonselective inhibitor of cathepsins K, L, V, and S[11] for which no clinical information has been published.

Odanacatib is a specific, potent, orally bioavailable CatK inhibitor that retains its selectivity in cell-based assays. It reduces bone resorption via a mechanism distinct from those of all currently available osteoporosis drugs.[12] Whereas other antiresorptive drugs decrease osteoclast activity, and some reduce the number of osteoclasts, ODN permits persistent osteoclast viability and cellular activity, including acid secretion, while selectively inhibiting the removal of matrix protein. The purpose of this study was to obtain additional safety data and to assess the dose response for BMD and bone turnover in postmenopausal women with low bone mass.

Materials and Methods

Study design

Odanacatib protocol 4 was a multicenter, double-blind, randomized, placebo-controlled 12-month study with a planned extension to 24 months. Thirty-six centers in North and South America, Europe, Australia, and New Zealand participated in the study from June 2005 through February 2008. The study was conducted in accordance with principles of good clinical practice and was approved by the appropriate institutional review boards and regulatory agencies. All participants provided written informed consent before any study procedures were performed, and a separate informed consent was obtained prior to bone biopsies in those participants from whom they were obtained. Dosages were selected after an initial dose-finding study using placebo and 5, 25, 50, and 100 mg of ODN weekly.[13]

After a 3-week placebo run-in period, eligible participants were assigned, using a computer-generated randomized allocation schedule generated by the study sponsor, to one of five treatment groups: placebo or 3, 10, 25, or 50 mg weekly of ODN taken without regard to the timing of meals. Treatment assignments were maintained throughout the 2 years of the trial. Starting with the run-in period, participants were provided with supplemental vitamin D_3 (5600 IU once weekly), and calcium (500 mg/day as calcium carbonate) was given to women whose average daily calcium intakes were less than 1000 mg from all sources. Data were collected on bone density, biochemical indices of skeletal remodeling, 24-hour urine calcium, adverse experiences (AEs), safety laboratory values, electrocardiograms, concomitant medications, and compliance, as monitored by participant recording of study medication and vitamin D_3 doses in calendar diary cards. The sponsor, investigative staff, technicians, and participants were blinded to treatment assignment throughout the 12-month base study. The investigators, participants, central laboratory (PPD, Highland Heights, KY, USA), and BMD quality assurance center (Synarc, Inc., Portland, OR, USA) remained blinded to treatment allocation throughout the entire 12-month extension period, but sponsor blinding was not maintained after 12-month analyses were conducted. A data safety monitoring committee with no involvement in study conduct was established to perform unblinded safety assessments at 3-month intervals.

Participants

Participants were community-dwelling, ambulatory, postmenopausal women ($\geq$5 years from cessation of menses or bilateral oophorectomy) between 45 and 85 years of age with a BMD *T*-score of -2.0 or less at the lumbar spine (L_1 to L_4), femoral neck, trochanter, or total hip but not less than -3.5 at any site. The women were otherwise required to be in good general health, with hip and spinal anatomy suitable for dual-energy X-ray absorptiometry (DXA) and with no history of prior hip, spine, or other fragility fracture since menopause. Baseline plain X-ray films of the thoracic and lumbar spine were obtained to exclude the presence of a prior vertebral fracture. Women with hypocalcemia, marked hypovitaminosis D (serum 25-hydroxyvitamin D $<$ 9 ng/mL, $<$ 22.5 nmol/L), or metabolic bone diseases other than postmenopausal osteopenia or osteoporosis were excluded. Other conditions resulting in exclusion were primary or secondary hyperparathyroidism and other metabolic bone disorders, as well as cancer or a diagnosis of any malignancy within the last 5 years, except for adequately treated skin cancer or in situ cervical cancer. Prospective participants also were excluded if they had ever used intravenous bisphosphonates or if they had used oral bisphosphonates within the prior 6 months or for 2 or more weeks in the 12 months before randomization; otherwise, exposure was limited to 2 months within the prior 2 years, 3 months within the prior 3 years, or 4 months within the prior 4 years. Use of estrogens, estrogen analogues, or selective estrogen receptor modulators was not allowed within the previous 6 months, nor was use of parathyroid hormone within the previous 12 months. Women who had used anabolic steroids or glucocorticoids ($\geq$5 mg/day prednisone or equivalent) or cyclosporine for more than 2 weeks in the prior 6 months also were excluded. Other medications resulting in patient exclusion were fluoride treatment at a dose greater than 1 mg/day for more than 2 weeks at any time; strontium (at any time); current use of phenytoin, chemotherapy, or heparin; use of growth hormone at any time; or use of vitamin A (excluding β-carotene) greater than 10,000 IU daily or vitamin D greater than 5000 IU daily. All women who satisfactorily completed the 12-month base study were eligible to enter the extension study.

Hypotheses

The primary hypotheses for the respective study periods were that ODN would increase lumbar spine BMD compared with placebo over 12 months (base study) and over 24 months (extension).

Endpoints

The primary endpoint was the percentage change from baseline in lumbar spine BMD. Percentage change from baseline BMD at the total hip, femoral neck, trochanter, total body, and one-third

radius were secondary endpoints. Other secondary endpoints included percentage change from baseline in biochemical indices of bone resorption [urinary *N*-telopeptides of type 1 collagen/creatinine ratio (uNTx/Cr), serum C-telopeptides of type 1 collagen (sCTx), urinary total deoxypyridinolines/creatinine ratio (uDPD/Cr)] and bone formation [serum bone-specific alkaline phosphatase (sBSAP) and serum N-terminal propeptides of type 1 collagen (sP1NP)]. Percentage change from baseline in tartrate-resistant acid phosphatase 5b (TRAP5b) was added as an exploratory endpoint before data analysis. The primary time points of interest were month 12 in the base study and month 24 in the extension. Safety and tolerability were assessed by a clinical review of all AEs and laboratory safety parameters. In addition, transilial biopsies obtained from all consenting participants at the end of 24 months were assessed histologically and by histomorphometry for bone safety, remodeling rate, mineralization, and microarchitecture. Indices of serum calcium and serum mineral homeostasis (s-calcium, s-phosphorus, s-parathyroid hormone, and s-1,25-dihydroxyvitamin D) also were measured.

Efficacy measurements

Bone Densitometry

BMD was measured by DXA at the lumbar spine, femur (total hip, femoral neck, trochanter), and one-third radius at randomization and at months 1, 3, 6, 12, 18, and 24. GE (Buckinghamshire, UK) Lunar and Hologic (Bedford, MA, USA) instruments were used by the various sites. These measurements were performed in duplicate at baseline and at 12 months. Total-body BMD was measured at randomization and at months 6, 12, and 24. All BMD data were centrally interpreted by the BMD quality assurance center, which also confirmed participant eligibility. A "gold standard" phantom was circulated to all sites at baseline and annually as part of a quality control program that also included monitoring of individual site precision. All BMD measurements were obtained from the same limb or from at least three vertebrae. For BMD at the lumbar spine, one-third radius, and femoral sites, baseline values were computed averages of two measurements obtained at the screening and randomization visits. Bone densitometry results at the follow-up visits were blinded to participants and investigators. At month 12, two BMD measurements were obtained for lumbar spine, one-third radius, and femoral sites, and only one was collected for the total body; the average of the two month-12 values was used in the analysis. At month 24, only one BMD measurement was collected at each anatomic site.

Serum and Urine Biochemistry

Participants provided fasting blood samples and a second morning voided urine specimen for measurement of bone biomarkers at week 1 and months 1, 3, 6, 12, 18, and 24. Individual biomarkers were assayed as follows: uNTx/Cr, OSTEOMARK assay (Ostex, Inc., Seattle, WA, USA); sCTx, Serum Crosslaps (Nordic Biosciences, Herlev, Denmark); uDPD/Cr, reverse-phase HPLC using isocratic elution; serum TRAP5b, BoneTRAP (SBA Sciences, Oulu, Finland); sBSAP, immunochemiluminescence assay using the Ostase reagent on an automatic analyzer (Access, Beckman Coulter, Fullerton, CA, USA); and P1NP, intact P1NP (^{125}I) RIA kit (Orion Diagnostica, Espoo, Finland). Analyses were performed by Synarc (Lyon, France). Baseline values used in the analyses were the last measurement for the variable obtained prior to administration of blinded study therapy. Samples were available for measurement of TRAP5b for only about half the participants and were not complete for Month 12. There was apparent drift of the assay between the batched assay for the first 6 months and the batch for months 18 and 24. Therefore, the results are summarized in relation to the placebo group for each time point except month 12.

Safety measurements

Clinical evaluations and laboratory measurements including serum chemistry, hematology, and urinalysis were performed at baseline and months 1 and 3 and then every 3 months until 24 months. A 24-hour urine collection for calcium was obtained at baseline and months 3 and 6 for a subset of participants. AEs were monitored throughout the study and up to 14 days after the last dose of study medication.

Bone Histomorphometry

Bone biopsies were obtained from 32 trial participants at 12 of the participating sites near the end of the second year on treatment. Procedures for fluorochrome double labeling, biopsy sample handling, qualitative histologic analysis, and quantitative histomorphometric analysis were performed as described by Recker and colleagues.[14] Transilial bone biopsies were evaluated histologically (Creighton University Histomorphometry Laboratory, Omaha, NE, USA) for evidence of possible drug-induced abnormalities, including woven bone and mineralization abnormalities. All personnel reading and interpreting the specimens were blinded to treatment group allocation. Endpoints for dynamic histomorphometric evaluation were activation frequency, mineralizing surface, mineralizing surface/osteoid surface, mineral apposition rate, mineralization lag time, osteoid surface/bone surface, osteoid thickness, bone-formation rate (total surface and bone volume referents), eroded (resorption) surface, osteoclast surface/bone surface, cortical thickness, and wall thickness. Appropriate raw data were collected using semiautomated histomorphometric methods, and all were calculated as described previously.[14]

Statistical methods

Participant data were analyzed according to treatment assignment at randomization regardless of actual treatment received (full analysis set) for the primary analyses. Data from all randomized participants in the base study who took at least one dose of blinded study therapy were included; in the extension analyses, participants who took at least one dose of extension medication were included. Missing data were imputed by carrying the latest measurement forward; no data were carried forward from the base study to the extension period. Analyses of biochemical indices of skeletal remodeling were performed using the per-protocol approach.

For planning purposes, an interim analysis was performed by sponsor personnel not involved in the conduct of the study after approximately 375 women completed 6 months of treatment. A conservative Hochberg-like approach[15] was used for the multiplicity adjustment for this interim analysis at month 12. No multiplicity adjustment was applied to the month 24 analysis or to safety analyses.

The primary endpoints of percentage change from baseline lumbar spine BMD at months 12 and 24 were analyzed using an analysis of covariance (ANCOVA) model with terms for treatment and study center. The primary and secondary BMD endpoints were analyzed using a stepwise linear trend test based on the ANCOVA model. The treatment effect was assessed by evaluating the within- and between-treatment group least-squares means (LS means) and the associated 95% confidence intervals. Because of the numerical differences between the data generated by the different instrument types, the results were expressed as percent change from baseline.

The log-transformed fraction of baseline value was analyzed for the biochemical markers of bone resorption (uNTx/Cr, sCTX, and uDPD/Cr) and bone formation (sBSAP and sP1NP) at months 12 and 24. Summary statistics were calculated and back-transformed for presentation (geometric mean percentage change from baseline). The log-transformed fraction from baseline was analyzed using a similar ANCOVA model as for the primary endpoint. The delta method was used to back-transform the between-treatment group LS means and associated 95% confidence intervals.

Power Estimate

Assuming 75 participants per group randomized into the base study and 10% discontinuation rates for the base and extension periods, there would be 80% power to detect (at the $\alpha = 0.050$ level, two-sided test) a between-group difference of 1.7% from baseline lumbar spine BMD at month 12 and 80% power to detect a between-group difference of 2.2% at month 24. The actual power for the three highest ODN doses for both periods was greater than 99% (two-sided test, $\alpha = 0.05$, n per group $= 60$, common SD $= 3.7$, detectable difference $\geq 3\%$).

Safety Analyses

The overall safety and tolerability of ODN compared with placebo were assessed by clinical and statistical review of all safety data, including AEs (with special attention to skin disorders and upper respiratory infections), laboratory safety parameters, electrocardiograms, and vital signs. All women who took at least one dose of study medication were included in the safety analyses. Missing data were not imputed. All AEs that occurred after the start of double-blind treatment and within 14 days after the last intake of double-blind study medication were included in the analyses. Comparisons of proportions of participants were performed using 95% confidence intervals for the between-group differences using Wilson's score method[16] for skin disorders, summaries of AEs, and specific AEs with incidence of at least 5% in one of the treatment groups.

Bone remodeling and histomorphometric analyses included summary statistics of the within-group values at month 24. The number of individuals in each group reflects the number of participants who volunteered to undergo the biopsy procedure. In view of this and the small number of biopsies available, only descriptive statistics are presented.

Results

Participant accounting

Of the 857 women screened for inclusion in the study, 458 (53%) women were excluded during screening owing to predetermined exclusion criteria (Fig. 1). The remaining 399 participants, who met the inclusion criteria, were randomly allocated to treatment. A total of 331 (83%) women completed the 12-month base study, 320 (80%) entered the 12-month extension study, and 280 (70%) completed 2 years.

A total of 66 (16%) participants discontinued early and did not complete 12 months of treatment. Two women did not complete their 12-month visits in time for inclusion in the 12-month analyses but entered the second year of the trial and are included in the 320 women who continued. There were no meaningful differences among the treatment groups in the percentage of participants who completed the base study. Reasons for early discontinuation were similar among treatment groups, with the following exception: The number of women discontinuing owing to clinical and laboratory AEs was slightly higher in the placebo and ODN 3-mg groups than in the 25- and 50-mg groups. A total of 40 women (12%) discontinued from the extension study and did not complete 24 months of treatment. The reasons for discontinuation were similar to those for the base study participants.

Participant demographics and baseline characteristics

In general, treatment groups were similar with respect to all baseline characteristics (Table 1) and were well balanced with respect to baseline risk factors and fracture history. For all groups, the mean serum 25-hydroxyvitamin D level $\pm$ SD was 30.5 $\pm$12.8 ng/mL. For the individual treatment groups, the means ranged from 28.9 to 31.9 ng/mL with similar SDs (11.5 to 16.2 ng/mL). For all groups, the mean serum iPTH level $\pm$ SD was 46.2 $\pm$ 15.9 pg/mL. For the individual treatment groups, the means ranged from 43.5 to 49.1 pg/mL with similar SDs (13.6 to 18.4 pg/mL).

Efficacy results

Compliance was very high (>98%) and was similar among all groups.

Bone Mineral Density

Treatment with 10, 25, or 50 mg of ODN once weekly for 12 months resulted in progressive dose-related increases in BMD from baseline for lumbar spine (Fig. 2*A*) and all femoral sites (Fig. 2*B*, *C*, trochanter not shown) that further increased through 24 months. In contrast, the mean BMD from baseline was either unchanged or decreased for the control (placebo tablet/calcium/vitamin D) and 3-mg groups. One-third radius BMD decreased from baseline at 24 months after treatment with control, 3 mg, or 10 mg of ODN but was maintained in the 25- and 50-mg groups

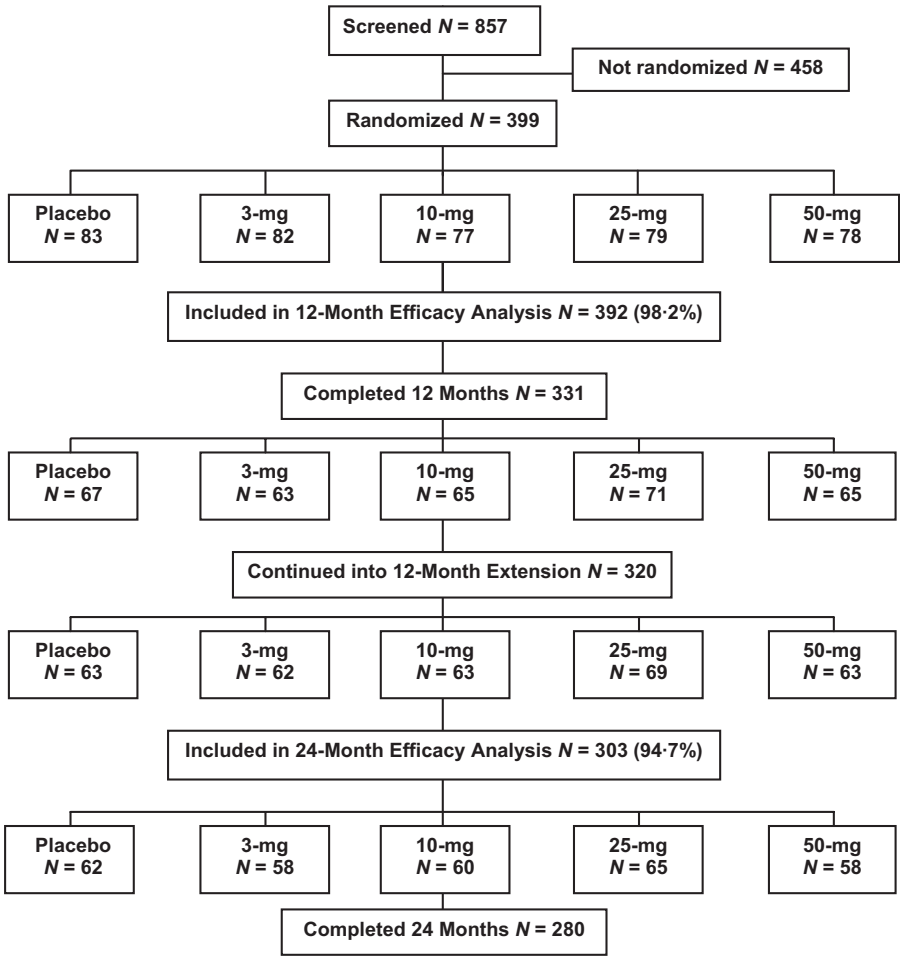

Fig. 1. Participant accounting. All groups received calcium and vitamin D.

(Fig. 2*D*). Total-body BMD decreased from baseline to month 24 for the control (−1.5%), 3-mg (−2.7%), and 10-mg (−1.3%) groups, whereas it remained relatively stable for the 25- (−0.4%) and 50-mg (0.2%) groups.

The 50-mg dose resulted in increases in BMD versus control of 5.7% for lumbar spine, 4.1% for total hip, 4.7% for femoral neck, 5.1% for trochanter, and 2.9% for one-third radius. Significant differences from control were seen for the 50- and 25-mg doses at months 12 and 24 for all BMD endpoints except total-body BMD. Analyses performed using the per-protocol approach were consistent with these results.

Table 1. Participant Baseline Characteristics

			Odanacatib					
	Placebo, $n = 83$	3 mg, $n = 82$	10 mg, $n = 77$	25 mg, $n = 79$	50 mg, $n = 78$	Included in base study, $n = 399$	Included in extension, $n = 320$	Women who discontinued, $n = 79$
Age (years)[a]	65.9 ± 7.8	63.1 ± 7.3	64.5 ± 8.0	62.9 ± 7.4	64.5 ± 8.1	64.2 ± 7.8	64.0 ± 7.7	64.8 ± 8.2
Years since menopause[a]	18.8 ± 8.4	16.1 ± 9.4	16.5 ± 10.3	17.7 ± 9.9	16.8 ± 9.7	17.2 ± 9.5	17.2 ± 9.4	17.1 ± 10.1
Race (% white)	79.5	78.0	77.9	75.9	74.4	77.2	75.3	84.8
T-scores[a]								
Lumbar spine	−2.1 ± 0.7	−2.2 ± 0.7	−2.2 ± 0.8	−2.1 ± 0.8	−2.1 ± 0.9	−2.2 ± 0.8	−2.2 ± 0.8	−2.1 ± 0.8
Total hip	−1.5 ± 0.6	−1.6 ± 0.8	−1.4 ± 0.7	−1.6 ± 0.8	−1.7 ± 0.7	−1.6 ± 0.7	−1.5 ± 0.7	−1.6 ± 0.7
Femoral neck	−1.9 ± 0.6	−1.8 ± 0.8	−1.8 ± 0.6	−1.9 ± 0.7	−2.0 ± 0.6	−1.9 ± 0.7	−1.9 ± 0.7	−1.9 ± 0.6
Trochanter	−1.3 ± 0.7	−1.3 ± 0.9	−1.2 ± 0.7	−1.3 ± 0.8	−1.3 ± 0.7	−1.3 ± 0.8	−1.3 ± 0.8	−1.4 ± 0.7
One-third radius	−2.9 ± 1.4	−2.6 ± 1.5	−2.6 ± 1.3	−2.7 ± 1.5	−2.7 ± 1.5	−2.7 ± 1.4	−2.7 ± 1.4	−2.7 ± 1.4

[a]Mean ± standard deviation.

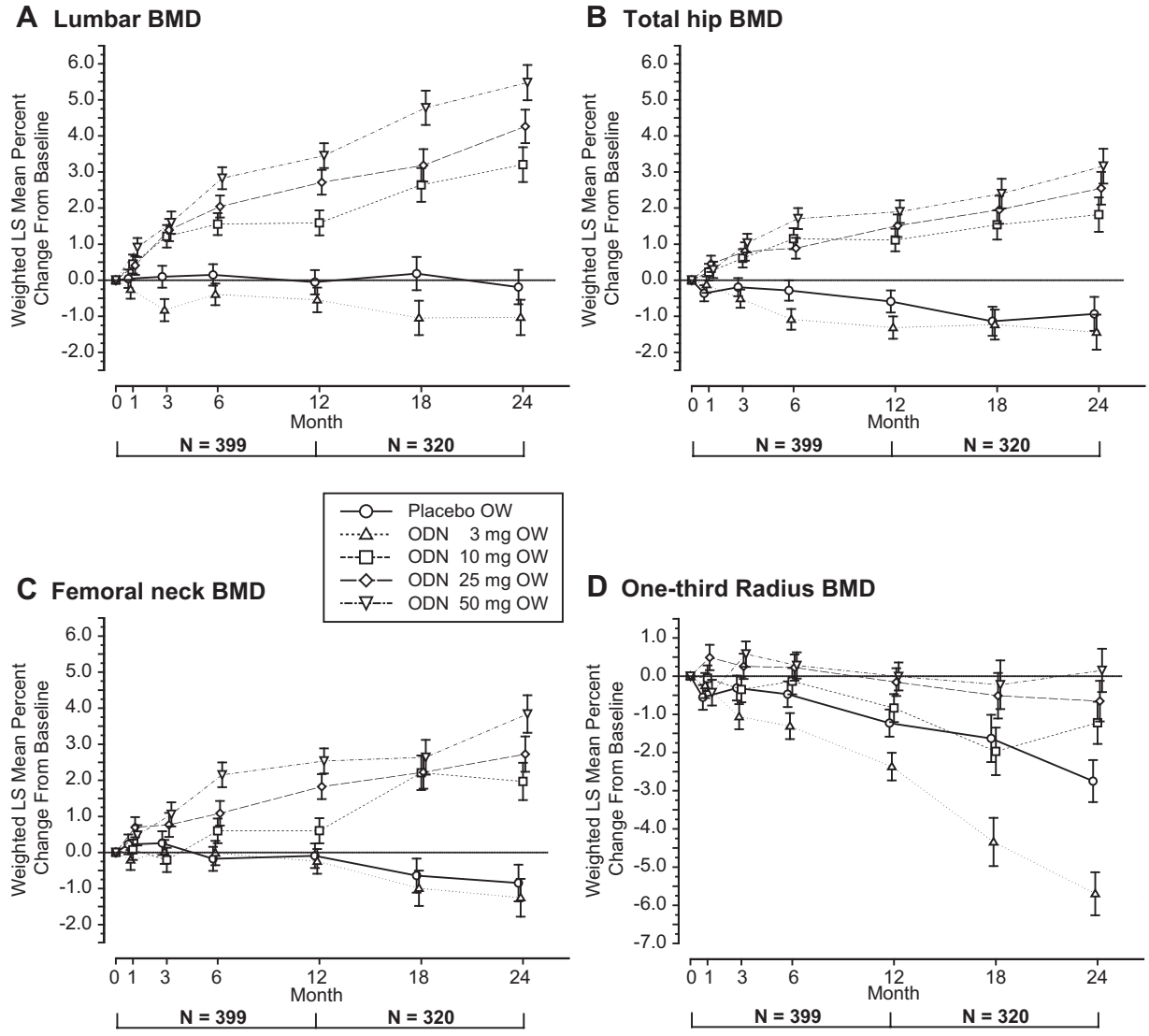

Fig. 2. BMD endpoints. Graphic presentation of the mean percentage change from baseline over 24 months in BMD at the specified site for the five treatment groups in the full-analysis-set population: (*A*) lumbar spine, (*B*) total hip, (*C*) femoral neck, (*D*) one-third radius.

Bone Resorption Markers

Treatment with 10, 25, and 50 mg of ODN for 24 months decreased levels of bone resorption markers compared with baseline. Mean uNTx/Cr levels (Fig. 3*A*) were essentially unchanged for the control group, increased for the 3-mg group, and decreased in the first few weeks and then remained relatively stable for the 10-, 25-, and 50-mg groups (12 months: −60.2%; 24 months: −51.8%) through month 24. Mean sCTx levels (Fig. 3*B*) were essentially unchanged for the control group through 12 months but increased thereafter and increased above baseline for the 3-mg group. In the three higher-dose groups, sCTx levels decreased in the first few weeks and then increased progressively toward baseline through month 24. At month 24, levels of sCTX in the three higher-dose groups remained lower than those seen in the control group. Mean uDPD/Cr levels (Fig. 3*C*) decreased in the first few weeks for the three higher-dose groups and returned to near-baseline values from month 6 onward for the 10-mg group and from month 12 onward for the 25-mg group but remained below baseline for the 50-mg group through 24 months. Significant differences from control were observed for the top three doses at 12 and 24 months for uNTx/Cr ($p \leq .001$), for the 50- and 25-mg doses at 12 and 24 months for sCTx ($p \leq .001$), and for the 50-mg dose at 12 months ($p = .004$) and 24 months ($p = .015$) for uDPD/Cr. There was a dose-related decrease from baseline in TRAP5b at week 1 (−20% in the 50-mg group, $p < .001$). The decrease diminished by the end of month 1 (−10% in the 50-mg group, $p < .001$) and resolved by the end of month 3. At months 18 and 24, TRAP5b was similar in all ODN treatment groups and up to 15% higher than in the control group ($p =$ NS).

Bone-Formation Markers

Treatment with 10, 25, and 50 mg of ODN resulted in initial decreases in levels of the bone-formation markers sBSAP

Table 2. Adverse Experiences Through 24 Months[a]

	Placebo OW ($n = 83$)	ODN 3 mg OW ($n = 82$)	ODN 10 mg OW ($n = 77$)	ODN 25 mg OW ($n = 79$)	ODN 50 mg OW ($n = 78$)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Clinical AE	77 (92.8)	76 (92.7)	73 (94.8)	72 (91.1)	72 (92.3)
Serious clinical AE	8 (9.6)	12 (14.6)	10 (13.0)	9 (11.4)	14 (17.9)
Skin AE	19 (22.9)	18 (22.0)	16 (20.8)	20 (25.3)	19 (24.4)
Upper respiratory tract AE[b]	9 (10.8)	10 (12.2)	9 (11.7)	8 (10.1)	10 (12.8)
Discontinued owing to AE	11 (13.3)	13 (15.9)	13 (16.9)	6 (7.6)	13 (16.7)
Discontinued owing to serious AE	0	2 (2.4)	3 (3.9)	1 (1.3)	3(3.8)
Discontinued owing to skin AE	2 (2.4)	3 (3.7)	2 (2.6)	0	4 (5.1)

[a]Includes all AEs that occurred after the start of the core study medication up to 14 days after the last dose of core or extension medication for all patients who took at least one dose of core or extension medication. It should be noted that for patients not continuing into the extension, the period of observation was only 1 year, whereas for others, it was 2 years.

[b]Upper respiratory tract infection includes respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, and viral upper respiratory tract infection. AE = adverse experience; ODN = odanacatib; OW = once weekly; serious AE is defined as any adverse experience that results in death, is life-threatening, results in significant disability/incapacity, or results in an inpatient hospitalization.

and sP1NP (Fig. 3*D*, *E*) for the first 6 months, followed by gradual increases thereafter. The control group was relatively unchanged from baseline to month 24 for both markers, and the 3-mg group increased from baseline, leveling off after month 12. At months 12 and 24, the control, 10-mg, and 25-mg groups showed little change in either biomarker. In the 50-mg group, sBSAP and P1NP decreased initially but then increased gradually somewhat from month 6 onward (P1NP: 12 months: −31.8; 24 months: −20.2). Significant differences from control for both sBSAP and sP1NP were observed only for the 50-mg group at month 12 ($p \leq .001$ for both) and month 24 (sBSAP: $p = .002$; P1NP: $p = .011$).

Safety results

All 399 randomized participants in the base study were included in the 12-month safety population. Clinical AEs were reported for 338 (84.7%) of the 399 participants, and laboratory AEs were reported for 40 (10.0%) participants. The overall incidences of clinical and laboratory AEs and discontinuations owing to AEs were similar across treatment groups, as were the incidences

Table 3. Transilial Biopsy Results at 24 Months

			ODN			
Variable	Units	Placebo, $n = 6$	3 mg, $n = 7$	10 mg, $n = 5$	25 mg, $n = 6$	50 mg, $n = 4$
Activation frequency	/yr	0.50 ± 0.16	0.66 ± 0.15	0.24 ± 0.07	0.34 ± 0.07	0.42 ± 0.17[a]
Mineralizing surface	%	6.92 ± 1.91	8.92 ± 1.87	3.26 ± 0.79	4.63 ± 1.06	4.70 ± 2.28
Mineralizing surface/ osteoid surface	%	62.8 ± 18.3	81.6 ± 21.9	53.9 ± 10.5	62.8 ± 10.8	42.5 ± 25.3
Mineral apposition rate	μm/day	0.53 ± 0.02	0.53 ± 0.04	0.53 ± 0.05	0.59 ± 0.04	0.51 ± 0.03[a]
Mineralization lag time	days	27.3 ± 7.7	17.4 ± 3.3	19.3 ± 4.6	15.2 ± 2.2	31.8 ± 11.9[a]
Osteoid surface/bone surface	%	12.17 ± 2.22	13.16 ± 2.58	6.33 ± 1.28	8.18 ± 2.43	10.37 ± 4.07
Osteoid thickness	μm	5.9 ± 0.5	5.2 ± 0.3	4.3 ± 0.2	4.9 ± 0.2	5.1 ± 0.6
Bone-formation rate (surface referent)	$\mu m^3/\mu m^2$/day	0.037 ± 0.011	0.049 ± 0.010	0.017 ± 0.005	0.027 ± 0.006	0.033 ± 0.014[a]
Bone-formation rate (bone volume referent)	%/yr	13.4 ± 2.4	18.2 ± 3.2	14.8 ± 6.4	13.0 ± 3.9	6.7 ± 2.1[a]
Eroded (resorption) surface	%	1.49 ± 0.22	1.45 ± 0.31	1.22 ± 0.38	1.23 ± 0.11	2.04 ± 0.68
Osteoclast surface/bone surface	%	0.62 ± 0.10	0.58 ± 0.15	0.43 ± 0.16	0.59 ± 0.10	0.60 ± 0.20
Cortical thickness	μm	873 ± 165	694 ± 76	855 ± 161	754 ± 85	940 ± 119
Wall thickness	μm	28.1 ± 0.7	27.4 ± 0.5	26.9 ± 0.9	28.6 ± 0.9	27.98 ± 0.7

All values are mean ± standard error.

[a]$n = 3$ for these endpoints in this group.

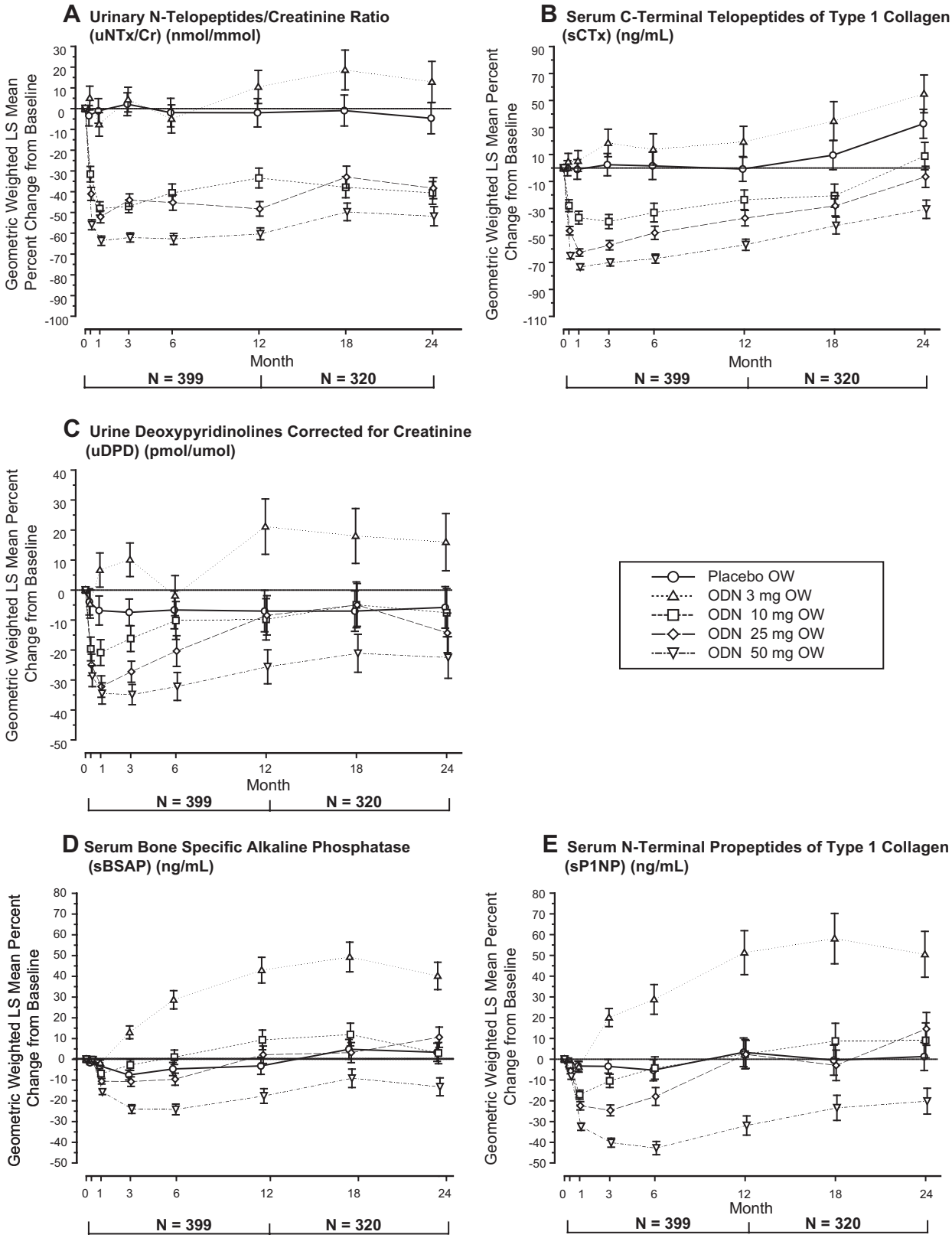

Fig. 3. Biochemical marker endpoints of bone resorption and bone formation. Graphic presentation of the geometric mean percentage change from baseline over 24 months for markers of bone resorption (*A*: uNTx/Cr; *B*: sCTx; *C*: uDPD/Cr) and bone formation (*D*: sBSAP; *E*: sP1NP) in the per-protocol population (back-transformed from log-transformed fraction from baseline).

of serious AEs and AEs thought by blinded investigators to be drug-related.

All 320 participants who entered the extension were included in the extension safety analysis. Only 50 (15.6%) participants had a laboratory AE; none was reported to be serious, and there was no evidence of a dose response. Overall, treatment did not result in any clinically important changes in calcium or mineral homeostasis. No clinical AEs were more common in the treatment arms (versus placebo) nor exhibited any dose response, even for the more commonly reported AEs of nausea, headache, and/or muscle spasm.

A summary of clinical AEs for all participants from the beginning of the base study through month 24 is shown in Table 2. Serious AEs leading to discontinuation were stomatitis and breast cancer in situ (3 mg); multiple myeloma/osteoporotic fracture, non-Hodgkin's lymphoma, and chest pain/hypertension (10 mg); anal cancer (25 mg); and chronic renal failure, papillary thyroid cancer/subsequent postoperative hypoparathyroidism, and sarcoma (50 mg). No pattern of treatment-emergent tolerability problems was apparent through 24 months.

In the context of reports of skin AEs and upper respiratory tract infections with another investigational CatK inhibitor, balacatib,[6] those AEs were monitored closely in this trial. Of the participants who reported a skin AE during the 24-month study period, there were no discernible patterns with respect to temporal relationship to study drug initiation, duration of symptoms, dermatologic diagnosis, or dose response across treatment groups. The most common skin AEs were those classified as rashes. These varied widely in clinical presentation. There were 9 patients with rash in the placebo group and 7, 5, 6, and 6 patients in the 3-, 10-, 25-, and 50-mg groups, respectively. There was one report of a serious skin AE (squamous cell carcinoma) in the 25-mg group; 11 women discontinued owing to skin AEs, but there was no apparent relationship to drug exposure. There were 28 and 39 reports of upper respiratory tract infection in the base study and the study extension, respectively, with no evidence for patterns with respect to time of onset, duration of symptoms, diagnosis, or dose response across treatment groups. No participants interrupted study therapy as a result of these reported symptoms.

Bone Biopsies

Thirty-two women consented to provide transilial biopsy samples at approximately 24 months; samples from four women were not evaluable owing to poor specimen quality. The qualitative assessment of the biopsies did not show any abnormalities, and none of the results on individual specimens departed significantly from the reference database. Giant osteoclasts were not observed. There appeared to be no clinically important differences among treatment groups for activation frequency, bone-formation rate, or osteoclast surface/bone surface ratio (Table 3). Sample size limited the power to determine the significance of small differences.

Discussion

Improvement of remodeling balance by inhibition of bone resorption is a well-established strategy for the treatment of osteoporosis. Emerging evidence suggests that the mechanism by which bone resorption is inhibited may influence the secondary effects on remodeling and potentially influence the response to stimulators of bone formation.[17] Odanacatib (ODN), by inhibiting cathepsin K activity within the remodeling space, decreases bone resorption but does not appear to reduce osteoclast number.[18]

At the higher ODN doses, there is a straightforward dose-response relationship between the effects on bone turnover and bone density. In this study population of postmenopausal women with low bone density, ODN treatment at doses of 10, 25, and 50 mg once weekly generally resulted in dose-dependent increases, compared with placebo, in lumbar spine, total-hip, femoral neck, trochanter, and one-third radius BMD. Substantial further increases in BMD were seen in the second year. The dose-dependent decreases in levels of uNTx/Cr and sCTx with the three higher doses are consistent with an antiresorptive effect. The general drift upward of sCTX in all treatment groups, including placebo, in year 2 at least in part may reflect a small change in assay calibration between the times the year 1 and year 2 assays were performed. Interpretation of changes in these bone resorption markers by ODN, however, may be different from the interpretation of these markers in women taking bisphosphonates or other drugs because of the direct role of CatK in the production of collagen fragments.[19–21] The mechanism for the early return of uDPD/Cr to baseline at doses of less than 50 mg weekly is unclear. Decreases in markers of bone formation were modest and transient compared with those seen with other antiresorptive therapies (e.g., alendronate and risedronate)[22,23] and are consistent with the nonsignificant decreases in bone-formation rate and mineralizing surface in the biopsy samples. TRAP5b is an index of osteoclast metabolic activity and cell number that is not directly related to collagen degradation. After an initial decrease on ODN treatment, TRAP5b levels recovered to those seen in the placebo group and remained at or slightly above those levels through 24 months, even in the 50-mg group. This differs dramatically from the large decreases in TRAP5b seen with other antiresorptive agents.[24–26] The TRAP5b data are consistent with bone biopsy findings, which show no effect of ODN on the osteoclast surface/bone surface ratio. They are also consistent with ODN's mechanism of action and with the possibility of a role for viable but ineffective osteoclasts in the regulation of bone remodeling. Taken together, the findings suggest that moderate effects on both resorption and formation result in a favorable effect on remodeling balance, as indicated by the progressive increase in BMD.

Results of treatment with the 3-mg dose of ODN were contrary to expectations and contrary to what was observed at the higher doses. There were small, nonsignificant decreases in lumbar spine, total-hip, femoral neck, and hip trochanter BMD and a larger and significant decrease in one-third radius BMD. The changes in bone remodeling markers and decrease in bone density measurements compared with placebo that were seen at this lowest dose remain difficult to explain. The increased turnover seen in the 3-mg group could be related to signaling effects of exposed matrix proteins or altered signaling by viable but ineffective osteoclasts. However, this dose is evidently not

adequate to produce a sustained antiresorptive effect sufficient to maintain a positive remodeling balance. In any case, the results are consistent with persistent viability of osteoclasts exposed to ODN and ultimately may provide insight into the mechanisms by which bone formation and bone resorption are regulated. These effects were not considered clinically significant in view of the modest osteopenia in these participants at baseline.

Two categories of AEs, skin AEs and upper respiratory tract infections, were specifically evaluated because of observations of an increased risk of these in a study of the CatK inhibitor balicatib.[6] There were no dose-related increases in the incidence of skin AEs in the ODN groups compared with placebo through 24 months. Likewise, no increase in the general category of upper respiratory tract infections was observed through 24 months. There was no pattern of clinical AEs across groups suggestive of a relationship to ODN dose. Taking into account the relatively small sample size and number of AEs of each category in each of the treatment groups and the small number of patients who discontinued owing to AEs, there does not appear to be any indication of drug-related toxicity.

The biopsy findings in this study gave no evidence of any skeletal toxicity. There were no observed dose-related trends. The number of samples in each group was small, so results should be interpreted with caution. Activation frequency and bone-formation rate did not appear to be reduced. Thus the gains in bone density are not associated with any apparent abnormality in bone histology or remodeling.

In summary, during 2 years of ODN treatment, there was a substantial and progressive increase in BMD in postmenopausal women with low BMD. There were modest effects on bone remodeling and no evidence of adverse histologic effects. ODN was generally well tolerated. These findings warrant further investigation of ODN for the treatment of osteoporosis.

Disclosures

HGB, as corresponding author, had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors met the ICJME criteria for authorship and were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data, drafting the manuscript, and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published.

HGB participated in the conception and design of the study, collected data, participated in the interpretion of the results and the writing of the initial and subsequent drafts, and has seen and approved of the final version. HGB served as a scientific advisor or consultant to Amgen, Merck, Zelos, Pfizer, GlaxoSmithKline, Novartis, Osteologix, Nordic Bioscience/Sanos, and Takeda Pharmaceuticals and received research support from Amgen, Merck, Zelos, Pfizer, Eli Lilly, Novartis, Nordic Bioscience, and Takeda Pharmaceuticals.

MRM participated in the design of the study, collected the data, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and has seen and approved of the final version. MRM served as a scientific advisor to and received research funding from Amgen, Lilly, Merck, Novartis, Procter & Gamble, and Sanofi-Aventis.

CR participated in the design of the study, collected the data, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and has seen and approved of the final version. CR received consulting or advisory board or lectures fees from Merck (MSD), Alliance of Bone Health, Novartis, Roche, Wyeth, Servier, Nycomed, and Amgen.

RRR participated in the design of the study, collected and assembled the data, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and has seen and approved of the final version. RRR was a paid consultant/speaker for Merck, Lilly, Wyeth, Procter & Gamble, Amgen, Roche, GlaxoSmithKline, Novartis, and NPS Allelix and has received grant/research support from Merck, Lilly, Wyeth, Procter & Gamble, Amgen, Roche, GlaxoSmithKline, Novartis, NPS Allelix, and Sanofi-Aventis.

JAE participated in the design of the study, collected the data, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and has seen and approved of the final version. JAE served as a scientific advisor or consultant to Amgen, deCode, Lilly, GE-Lunar, Merck, Novartis, Roche-GSK, Sanofi-Aventis, Servier, and Wyeth Australia and received research support from Amgen, Lilly, Merck, Novartis, Roche-GSK, Sanofi-Aventis, and Servier.

NV participated in the planning and design of the study, assembled the data, performed analyses, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and has seen and approved of the final version. NV is an employee of Merck & Co., Inc., and may potentially own stock and/or hold stock options in the company.

CMH participated in the interpretation of the results, wrote sections of the initial draft, provided substantive suggestions for revision on iterations of the draft manuscript, and has seen and approved of the final version. CMH is an employee of Merck & Co., Inc., and may potentially own stock and/or hold stock options in the company.

CDS participated in the planning and design of the study, collected and assembled the data, interpreted the results, wrote sections of the initial draft, and has seen and approved of the final version. CDS is an employee of Merck & Co., Inc., and may potentially own stock and/or hold stock options in the company.

ACS participated in the conception, planning, and design of the study, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and has seen and approved of the final version. ACS is an employee of Merck & Co., Inc., and may potentially own stock and/or hold stock options in the company.

BAI participated in the conception, planning, and design of the study, interpreted the results, wrote sections of the initial draft, provided substantive suggestions for revision on iterations of the draft manuscript, and has seen and approved of the final version. BAI is an employee of Merck & Co., Inc., and may potentially own stock and/or hold stock options in the company.

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