ORIGINAL ARTICLE

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Odanacatib in the Treatment of Postmenopausal Women With Low Bone Mineral Density: Three-Year Continued Therapy and Resolution of Effect

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ABSTRACT

The selective cathepsin K inhibitor odanacatib (ODN) progressively increased bone mineral density (BMD) and decreased bone-resorption markers during 2 years of treatment in postmenopausal women with low BMD. A 1-year extension study further assessed ODN efficacy and safety and the effects of discontinuing therapy. In the base study, postmenopausal women with BMD *T*-scores between −2.0 and −3.5 at the lumbar spine or femur received placebo or ODN 3, 10, 25, or 50 mg weekly. After 2 years, patients ($n = 189$) were rerandomized to ODN 50 mg weekly or placebo for an additional year. Endpoints included BMD at the lumbar spine (primary), total hip, and hip subregions; levels of bone turnover markers; and safety assessments. Continued treatment with 50 mg of ODN for 3 years produced significant increases from baseline and from year 2 in BMD at the spine (7.9% and 2.3%) and total hip (5.8% and 2.4%). Urine cross-linked *N*-telopeptide of type I collagen (NTx) remained suppressed at year 3 (−50.5%), but bone-specific alkaline phosphatase (BSAP) was relatively unchanged from baseline. Treatment discontinuation resulted in bone loss at all sites, but BMD remained at or above baseline. After ODN discontinuation at month 24, bone turnover markers increased transiently above baseline, but this increase largely resolved by month 36. There were similar overall adverse-event rates in both treatment groups. It is concluded that 3 years of ODN treatment resulted in progressive increases in BMD and was generally well tolerated. Bone-resorption markers remained suppressed, whereas bone-formation markers returned to near baseline. ODN effects were reversible: bone resorption increased transiently and BMD decreased following treatment discontinuation. © 2011 American Society for Bone and Mineral Research.

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

Introduction

Osteoporosis is a clinical condition of substantial and increasing importance. Approximately 30% of all postmenopausal women in the United States and Europe have osteoporosis, and the prevalence of this condition is expected to increase as the world population ages, resulting in rising health care costs.[1] Apart from supplements of calcium and vitamin D, current treatment options for osteoporosis include several bisphosphonates, estrogens, selective estrogen receptor modulators (SERMs), calcitonin, and teriparatide. Except for the latter, most of these treatments act primarily by globally suppressing osteoclast activity to decrease bone resorption and secondarily suppress osteoblast activity. This, in turn, results in attenuation of

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the rate of increase in bone mineral density (BMD). In addition, there is some concern about possible oversuppression of bone remodeling with some of these agents. Thus there is a potential role for additional therapeutic mechanisms that more selectively inhibit osteoclast function.

Osteoclastic bone resorption involves demineralization of inorganic bone mineral followed by degradation of organic bone matrix. These processes occur via two separate mechanisms: the secretion of acid by the osteoclast into resorption lacunae on the bone surface, followed by degradation of organic (mainly proteinaceous) matrix, primarily by cathepsin K (catK), a cysteine protease produced by the osteoclast that exhibits collagenolytic activity under acidic conditions. Since catK is expressed primarily in osteoclasts, inhibition of this enzyme to reduce bone resorption is being explored as a pharmacologic treatment for osteoporosis.[2–7] Recent advances have led to the discovery of drugs that selectively inhibit either acid secretion[8–10] or catK activity.[2–5,11,12] Some early catK inhibitors proved to have cross-reactivity with other cathepsins,[5,13,14] and cutaneous adverse events were reported for one.[3,15] A highly selective catK inhibitor that affects osteoclast bone resorption activity without effects on other cell types, including osteoblasts, would be attractive as a treatment for osteoporosis.

Odanacatib (ODN) is a potent, orally active selective inhibitor of catK being developed for the treatment of postmenopausal osteoporosis. Treatment with ODN decreases bone resorption by selectively inhibiting proteolysis of matrix protein by catK without affecting other osteoclast activities or osteoclast viability.[6,7] A dose-ranging study in postmenopausal women with low BMD showed that ODN treatment progressively increased BMD, decreased bone-resorption biomarkers (with lesser effect on bone-formation biomarkers), did not suppress TRACP 5b, and was generally well tolerated over 2 years.[16] This study is a 1-year extension of that dose-ranging study. In this extension, patients were rerandomized to continued ODN therapy at the once-weekly 50-mg dose or switched to placebo in a 1:1 ratio. The purpose of this study extension was to investigate the efficacy of continued ODN treatment on BMD, biochemical markers of bone turnover, and safety and to examine the changes in BMD and bone biomarkers after discontinuing ODN following 2 years of treatment.

Methods

Study design

This was a 1-year extension (Protocol 004-10) to the 2-year dose-ranging study (Protocol 004-02).[16] The base study was a randomized, double-blind, placebo-controlled, multicenter worldwide study in which 399 postmenopausal women aged 45 to 85 years with osteoporosis [defined as a BMD *T*-score at the proximal femur (femoral neck, trochanter, or total) or lumbar spine of -2.0 or less but not less than -3.5] were randomly assigned to one of five treatment groups: ODN 3 mg, 10 mg, 25 mg, or 50 mg weekly or placebo tablets matching ODN. All participants received supplementation with open-label vitamin D_3, 5600 IU weekly, and those with total calcium intake (dietary + supplemental) of less than 1000 mg/day received open-label calcium supplements, 500 mg daily. Further details of the base-study design have been described previously.[16]

Women who completed 2 years of treatment in the base study and were in good health, based on medical history, physical examination, and laboratory evaluation, were given the opportunity to enter this extension. Thirty-one centers in 14 countries participated in the third year of the study: United States (9 sites), Austria (2 sites), Australia (1 site), Chile (1 site), Colombia (1 site), Denmark (2 sites), France (2 sites), Mexico (2 sites), New Zealand (2 sites), Norway (2 sites), Peru (2 sites), Sweden (1 site), Switzerland (2 sites), and United Kingdom (2 sites); five sites from the base study did not participate in the extension. The extension study was conducted in accordance with good clinical practice standards and was approved by the appropriate institutional review boards and regulatory agencies. All eligible participants provided an additional written informed consent before any extension study procedures were performed.

In this extension, patients in all treatment groups were rerandomized to either ODN 50 mg weekly or matching placebo (Fig. 1). Patients (and staff at investigational sites, the central laboratory, and the BMD quality-assurance center) remained blinded to the treatment received during the previous 2 years and to the treatment received in the extension. The sponsor was blinded to treatment-group allocation, laboratory, and BMD results after rerandomization in the extension until all patients completed 3 months of treatment in the extension. Investigators, patients, and study staff remain blinded as patients continue into a further 2-year extension of the study (years 4 and 5) to continue to assess long-term efficacy and safety. For years 4 and 5, women who received placebo or 3 mg ODN in years 1 and 2 and placebo in year 3 will switch to 50 mg ODN for years 4 and 5; all others will continue with their year 3 regimen. A data safety monitoring committee with no involvement in study conduct continues to perform unblinded safety assessments at 3-month intervals.

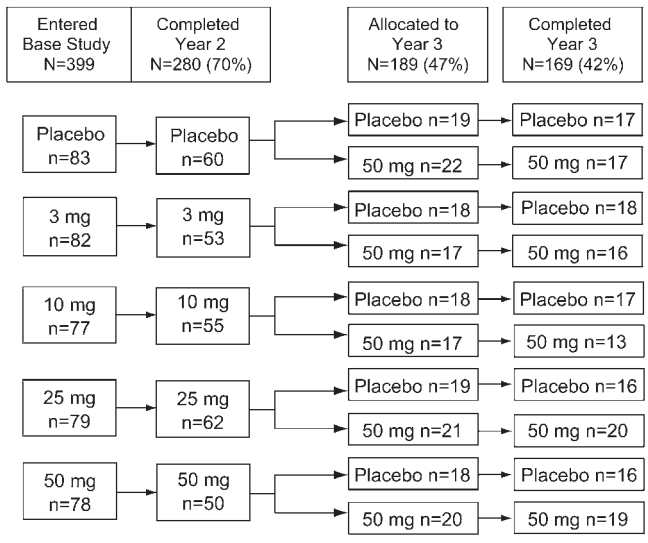

Fig. 1. Patient randomization in extension study.

Objectives

The primary objective of the extension was to assess the resolution of effect at 3 years on lumbar spine BMD following 2 years of treatment with ODN once weekly in postmenopausal women with low BMD. As secondary objectives, the study assessed the effect of continued treatment with ODN 50 mg weekly on BMD, biochemical markers, indices of calcium and mineral homeostasis, and safety; the resolution of effects at skeletal sites other than the spine; and the resolution of biochemical effects.

Endpoints

Measurements of BMD by dual-energy X-ray absorptiometry (DXA) at the lumbar spine, proximal femur (trochanter, femoral neck, total), 1/3 radius, and total body were performed at month 24 (last visit of base study) and at months 30 and 36. All BMD scans (which used the same limb and at least three vertebrae for all time points) were centrally evaluated. Biochemical markers of bone turnover [serum bone-specific alkaline phosphatase (s-BSAP), serum N–terminal propeptide of type 1 collagen (s-P1NP), urinary *N*-telopeptides of type 1 collagen/creatinine ratio (u-NTx/Cr), serum *C*–telopeptides of type 1 collagen (s-CTx), urinary total deoxypyridinolines (u-DPyr), serum cross-linked C-terminal telopeptide of type 1 collagen (s-1CTP), and serum tartrate-resistant acid phosphatase isoform 5b (s-TRACP 5b)] were measured in the fasting state at month 24 and at months 25, 27, 30, 33, and 36. Individual biomarker assays (Synarc, Lyon, France) were as described previously.[16] Samples for the first 2 years were assayed in one batch. The later time points were assayed in a different batch.

Indices of calcium and mineral homeostasis (calcium, phosphate, parathyroid hormone, and 1,25-dihydroxyvitamin D) were measured at months 24, 25, 30, 33, and 36. Clinical evaluations and laboratory measurements (by the central laboratory: PPD, Highland Heights, KY, USA) included serum chemistry, hematology, and urinalysis and were performed at month 24 and at months 27, 30, 33, and 36.

Safety was assessed by a clinical evaluation of adverse experiences (AEs) and inspection of other study parameters, including vital signs, physical examination, and laboratory measurements.

Statistical methods

All statistical analyses were performed by the study sponsor. This extension study was an estimation study, and no hypotheses were tested.

Efficacy

Efficacy endpoints were assessed in two ways: as the percentage change at year 3 compared with baseline at the start of the base study and as a percentage change between year 2 and year 3. Resolution of effect was assessed by percent change from baseline at year 3 for the patients who received ODN 50 mg for 3 years compared with those who received ODN 50 mg in the 2-year base period and switched to placebo for the third-year extension.

For BMD endpoints, between- and within-treatment least-squares (LS) means from an ANOVA model with terms for treatment and study center are presented together with their 95% confidence intervals (CIs). Long-term effects for all BMD endpoints were assessed by arithmetic mean percent change from baseline with time for all treatment groups, together with the within-treatment 95% CIs using both a full-analysis-set approach and a per-protocol approach, with no estimation of missing data. BMD changes from year 2 to year 3 and resolution of effect were assessed based on a per-protocol approach.

All analyses of biochemical markers of bone formation and bone resorption, as well as the indices of calcium and mineral homeostasis, were performed based on a per-protocol approach, with no estimation of missing data. Resolution of effect was assessed by geometric mean percent change from baseline at year 3 (backtransformation of the log-transformed fraction from baseline) using the same approach as for BMD endpoints.

Safety and tolerability

Safety and tolerability were assessed by a clinical review of all relevant AEs and laboratory safety parameters at the conclusion of the 3-year extension study; all AEs that occurred after the start of extension medication and within 14 days of the last intake of double-blind extension study medication were included in the analyses. For this 1-year extension period, all placebo subgroups were combined and all ODN 50-mg groups were combined for safety endpoints. Safety analyses were performed using the all-patients-as-treated population, including all patients who took at least one dose of extension medication, counted in the treatment group of the medication they actually took. Missing data were not imputed. The primary safety analysis focused on AEs, with special attention to skin disorders, based on reports with another catK inhibitor.[3,15] AEs were summarized by number (%) of patients within treatment groups for the 1-year extension period (from year 2 to year 3). Percentages of patients with at least one laboratory value outside the predefined limits of change during the 1-year extension period were summarized by treatment group and analyte.

Sample size and power

Approximately 285 patients were expected to participate in the extension, or approximately 30 from each of the 10 treatment groups in year 2. The power calculations consider two randomization groups: 50 mg/50 mg and 50 mg/placebo. Assuming that among patients who received ODN 50 mg in the 2-year treatment period, approximately 30 would switch to placebo and another 30 would remain on ODN 50 mg during year 3, and assuming a common SD of 3% in both groups, the width of the 95% CI for difference in LS means between 50 mg/50 mg and 50 mg/placebo groups in percent change from baseline in lumbar spine would be 3%. With a common SD of 3.5, this becomes 3.6%. Results of the statistical analysis showed that the SD actually was 4.4, so the width of the 95% CI for the difference in LS means for percent change from baseline in lumbar spine BMD between the two groups (50 mg/50 mg and 50 mg/placebo) was 6.2%.

Results

Patient demographics and baseline characteristics

Of the 280 women who completed 2 years of treatment in the base study, 189 (67.5%) were randomly assigned to either ODN 50 mg weekly ($n = 97$) or placebo ($n = 92$) in the extension (Fig. 1). The most common reasons for patients not continuing into the extension were withdrawal of consent (25 patients), discontinuation for other reasons (30 patients), and site declining participation in the extension (20 patients). Of the 189 extension participants, 169 (89.4%) completed the third year of treatment. Reasons for discontinuation from the extension were similar among treatment groups. All patients who completed the third year of treatment were included in the BMD efficacy analyses. All 189 women were included in the safety analyses. Baseline characteristics for those who entered into the extension generally were similar between treatment groups (Table 1); characteristics of the groups in each year of the study are shown in Supplemental Table S1. Compliance was greater than 97% and similar for both treatment groups.

Efficacy

The 50-mg ODN once-weekly dose is currently being tested in a large phase III fracture trial. For this reason, the data highlighted in this article are from women who received placebo for 3 years (Pbo/Pbo), those treated with 50 mg ODN for 3 years (ODN/ODN), and those treated with 50 mg ODN for 2 years and rerandomized to placebo in year 3 (ODN/Pbo) for the per-protocol population for all endpoints. Information about the other dosage groups can be found in the online supplement: Supplemental Table S2 shows changes from year 2, Supplemental Table S3 shows changes from baseline, and Supplemental Figs. S1 and S2 show graphs of BMD and bone biomarker changes by year 1 and year 2 dosage group. All graphs in this article and the supplement show data from only the extension patients at all time points; data for all patients through years 1 and 2 have been published previously.[16]

Table 1. Baseline Patient Characteristics of Women in Year 3 Extension

	Placebo ($N = 92$)		ODN 50 mg ($N = 97$)	
	n	%	*n*	%
Age (years)[a]				
<65	50	54.3	56	57.7
≥65	42	45.7	41	42.3
Mean (SD)	63.8 (8.2)		64.2 (6.9)	
Race				
Asian	1	1.1	0	
Black	1	1.1	0	
White	65	70.7	73	75.3
All others	25	27.2	24	24.7
Years since last menses				
Mean (SD)	16.7 (9.6)		18.4 (9.0)	
Age at last menses				
Mean (SD), years	47.1 (6.9)		45.8 (6.7)	
T-scores (mean ± SD)				
Lumbar spine	−2.2 ± 0.8		−2.2 ± 0.7	
Total hip	−1.5 ± 0.7		−1.4 ± 0.8	
Femoral neck	−1.8 ± 0.7		−1.8 ± 0.7	
Trochanter	−1.3 ± 0.7		−1.1 ± 0.8	

SD = Standard deviation.
[a]Age at baseline of base study.

BMD

Discontinuation of treatment with 50 mg ODN (ODN/Pbo) resulted in BMD decreases at all sites to levels that were not different from baseline at the end of year 3: at the lumbar spine (+1.4% versus baseline; 95% CI −0.8, 3.6; Fig. 2*A*), total hip (−0.5%; 95% CI −2.6, 1.6; Fig. 2*B*), trochanter (−0.7%; 95% CI −3.8, 2.5), or total body (−1.8%; 95% CI −4.0, 0.3). Values remained above baseline at the femoral neck (+2.3%; 95% CI 0.2, 4.3; Fig. 2*C*) but decreased to below baseline at 1/3 radius (−2.7%; 95% CI −5.2, −0.2). The rate of bone loss was faster in the initial 6 months following discontinuation of treatment than in the second 6 months.

Significant changes in BMD from year 2 to year 3 for those who continued taking 50 mg ODN in year 3 (ODN/ODN) were +2.3% for lumbar spine (95% CI 0.5, 4.2; Fig. 2*A*), +2.4% for total hip (95% CI 0.7, 4.0; Fig. 2*B*), +1.6% for femoral neck (95% CI 0.5, 2.7; Fig. 2*C*), and +2.7% for trochanter (95% CI 0.4, 5.0). Treatment with ODN 50 mg for a third year resulted in a cumulative increase from baseline to +7.9% (LS mean, 95% CI 5.7, 10.0) in lumbar spine BMD, +5.8% (95% CI 3.9, 7.8) in total-hip BMD, +5.0% (95% CI 3.0, 6.9) in femoral neck BMD, and +7.4% (95% CI 4.5, 10.4) in trochanter BMD after 3 years. There was no significant change over the third year for total-body BMD (+0.5%; 95% CI −0.03, 1.2) or for 1/3 radius BMD (−0.4%; 95% CI −2.0, 1.2). Moreover, there was no change from baseline for total-body BMD (−0.4%; 95% CI −2.4, 1.7) or 1/3 radius BMD (−0.3%; 95% CI −2.5, 2.0) with continued treatment with 50 mg ODN for a third year. Analyses of change in BMD endpoints from baseline using the per-protocol approach generally were consistent with those using the full-analysis-set approach.

Biochemical markers of bone resorption

Changes in levels of bone-resorption markers from year 2 to year 3 for those who continued taking 50 mg ODN in year 3 (ODN/ODN) were nonsignificant: −12% (95% CI −36, 21) for u-NTx/Cr (Fig. 3*A*), +1% (95% CI −27, 40) for s-CTx (Fig. 3*B*), and −26% (95% CI −57, 29) for u-Dpyr/Cr. Continued treatment with ODN 50 mg for a third year resulted in approximately 50% (95% CI −62, -35) suppression in u-NTx/Cr at year 3 compared with baseline; u-NTx decreased by 17% (95% CI −39, 12) for those who received placebo for 3 years. In patients receiving continued treatment with 50 mg ODN, s-CTx and u-Dpyr/Cr were suppressed in the first few months and returned approximately to the baseline value (s-CTx: −24%; 95% CI −44, 4; u-Dpyr/Cr: −17%; 95% CI −38, 12). In the placebo group, the changes were s-CTx −0.1% (95% CI −29, 40) and u-Dpyr/Cr −19% (95% CI −42, 13).

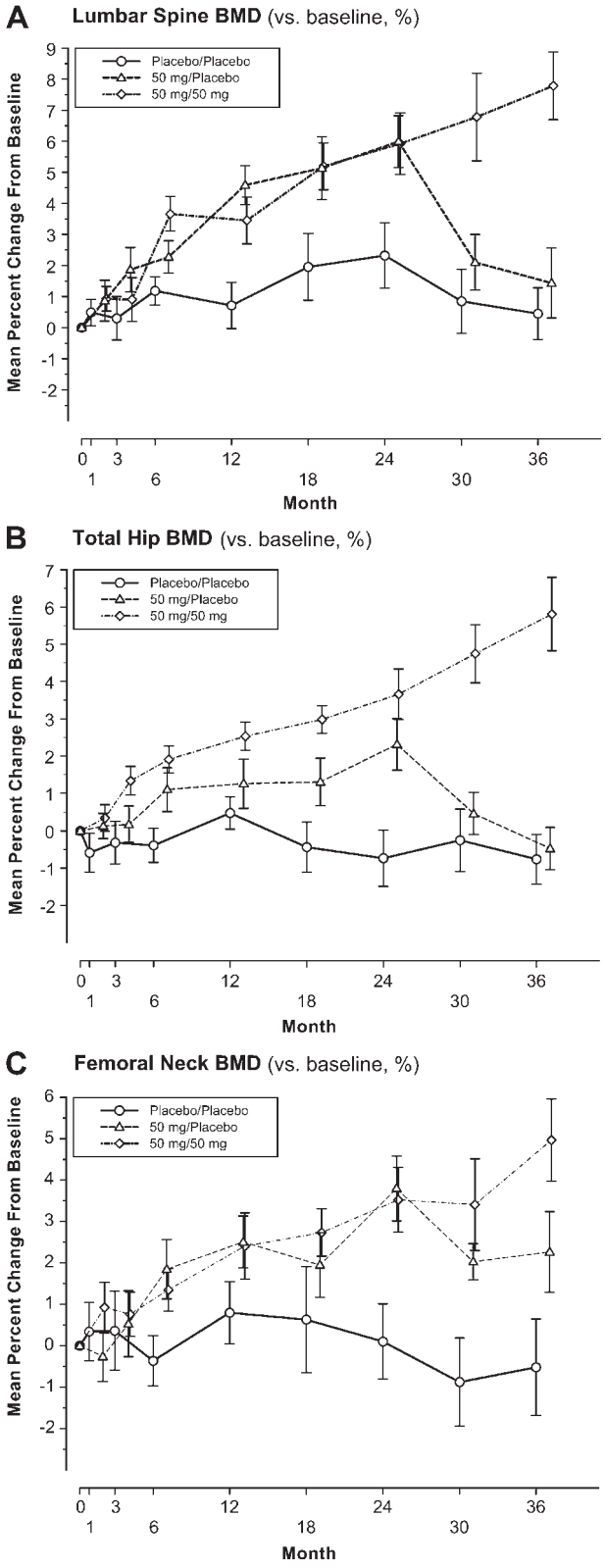

Fig. 2. BMD endpoints. Graphic presentation of the mean percentage change from baseline over 3 years in BMD at the specified site for the 50-mg/50-mg (ODN/ODN), 50-mg/placebo (ODN/Pbo), and placebo/placebo (Pbo/Pbo) treatment groups in the per-protocol extension population: (*A*) lumbar spine, (*B*) total hip, (*C*) femoral neck.

Discontinuation of treatment (ODN/Pbo) was associated with a rapid increase in the first month in u-NTx/Cr to values approximately 50% above the baseline value, followed by a resolution to within 28% (95% CI −6, 73) of baseline at the end of year 3 (Fig. 3*A*). A similar pattern of response was seen for s-CTx, with a rapid increase to approximately 120% above baseline that returned to within 10% (95% CI −22, 55) of baseline at the end of year 3 (Fig. 3*B*), and for u-Dpyr/Cr, with a rapid increase to approximately 90% above baseline that decreased to 22% (95% CI −12, 71) above baseline at the end of year 3.

TRACP 5b and 1CTP

TRACP 5b (Fig. 4*A*) and s-1CTP (Fig. 4*B*) were increased compared with baseline in patients continuing on ODN treatment for a third year (ODN/ODN). A similar increase in TRACP 5b was observed in the placebo group (Pbo/Pbo), but minimal change in 1CTP was observed in the placebo group over 3 years. Discontinuation of treatment (ODN/Pbo) resulted in decreases in TRACP 5b levels to placebo levels (LS mean change from baseline: 48%; 95% CI 25, 74) and in s-1CTP levels to mean values somewhat above baseline values (geometric LS mean change: 27%; 95% CI −1, 63).

Biochemical markers of bone formation

In patients continuously treated with ODN (ODN/ODN), both s-BSAP and s-P1NP decreased initially, reaching a plateau after approximately 6 months, but subsequently increased to above (s-BSAP: 18%; 95% CI 3, 35; Fig. 3*C*) or near baseline (s-P1NP: −6%; 95% CI −27, 21; Fig. 3*D*) by the end of year 3. Discontinuation of treatment (ODN/Pbo) led to an initial increase in s-BSAP (34%) and s-P1NP (90%) levels at month 30, which resolved back to baseline by the end of year 3.

Safety

For this 1-year extension period, all placebo subgroups were combined and all ODN 50-mg groups were combined for safety endpoints. Adverse experiences in Table 2 are only those which occurred after rerandomization at the end of year 2 and within 14 days of the last intake of double-blind study medication (in the third-year extension). Clinical AEs for all 3 years in each dosage group are shown in Supplemental Table S3. Clinical AEs were reported by 150 (79.4%) of the 189 extension participants. The most common clinical AEs, regardless of treatment group, were back pain (19 women, 10.1%), arthralgia (15 women, 7.9%), pain in an extremity (16 women, 8.5%), and nasopharyngitis (18 women, 9.5%). The incidence of AEs of any type generally was balanced between the 50-mg ODN and placebo groups (Table 2). In year 3, there was a disparity in the number of events reported and treated as urinary tract infections (UTIs) or cystitis between the active treatment group (12) and the placebo group (3). This is different from the results in the first 2 years, during which such events were well balanced among the groups. These AEs were reported by the participants at scheduled visits in connection with reports of concomitant medications taken since the last such visit, and no microbiologic confirmation was required. The diagnoses usually were made by the participant's primary physician on the basis of symptoms and/or urinalyses. Urine

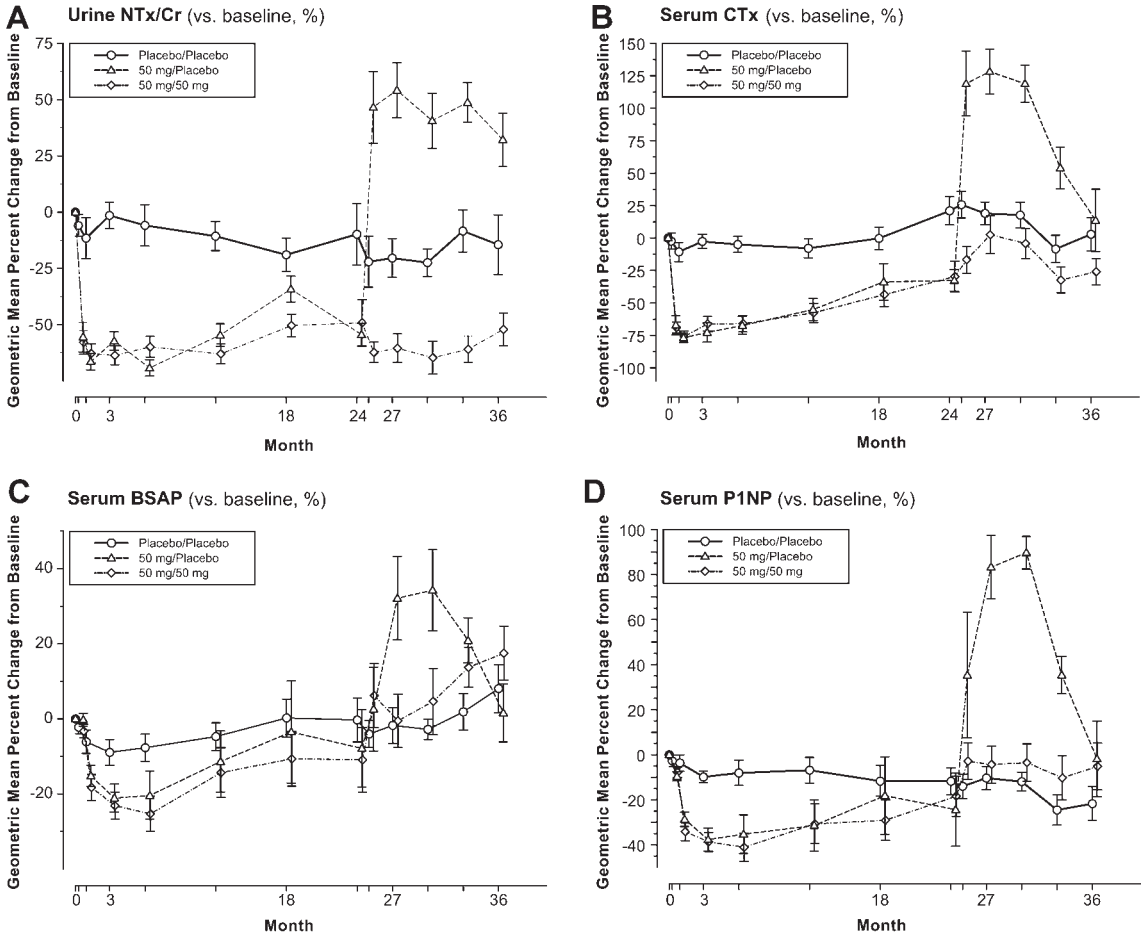

Fig. 3. Biochemical markers of bone resorption and bone formation. Graphic presentation of the geometric mean percentage change from baseline over 3 years for markers of bone resorption, (*A*) u-NTx/Cr, (*B*) s-CTx), and bone formation, (*C*) s-BSAP, (*D*) s-P1NP), for the 50-mg/50-mg (ODN/ODN), 50-mg/placebo (ODN/Pbo), and placebo/placebo (Pbo/Pbo) treatment groups in the per-protocol extension population (backtransformed from log-transformed fraction from baseline).

cultures were reported to have been obtained in only four instances (all in the active treatment group). On review, one culture was not performed, but automated analysis for white cells and bacteria indicated no evidence of UTI, two showed no growth, and only one culture was positive for more than 100,000 bacteria of a pathogenic species per milliliter. Seven events were symptomatic, with dysuria being the most common complaint. All events were rated as mild to moderate intensity and resolved following antibiotic therapy; the study drug was continued in all patients.

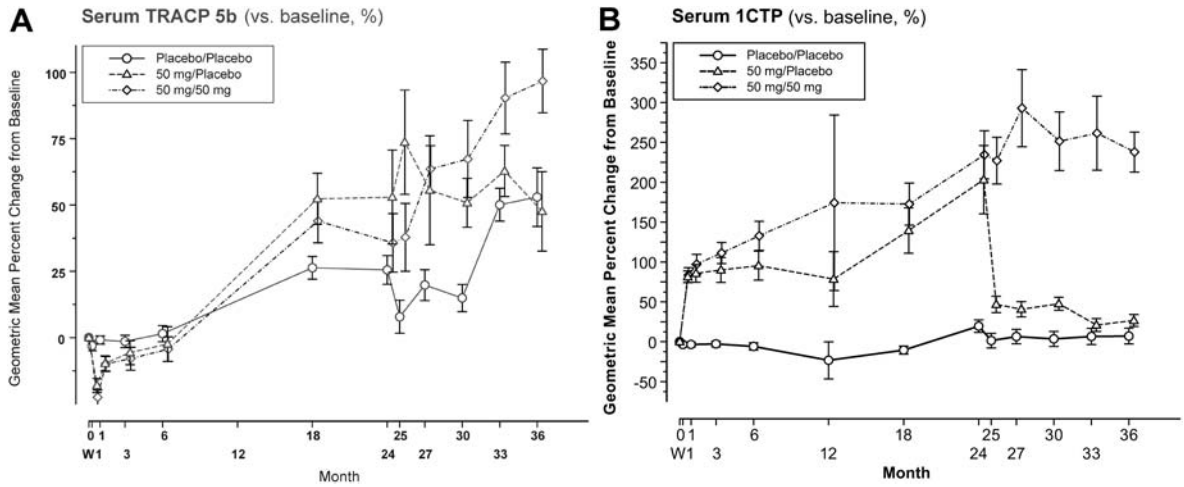

Fig. 4. Other bone turnover markers. Graphic presentation of the geometric mean percentage change from baseline over 3 years for serum TRACP 5b (*A*) and s-1CTP (*B*) in the per-protocol population (backtransformed from log-transformed fraction from baseline).

Table 2. Adverse Events in Year 3

Adverse events	Placebo pooled ($N = 92$) *n* (%)	ODN 50 mg pooled ($N = 97$) *n* (%)
Overall	74 (80)	76 (78)
Leading to discontinuation	4 (4)	4 (4)
Serious	8 (9)	10 (10)
Serious AE leading to discontinuation	0	1 (1)
Skin	15 (16)	12 (12)
Respiratory	7 (8)	7 (7)
Urinary tract infections/cystitis	3 (3)	12 (12)

A total of 18 (9%: 8 placebo, 10 ODN) participants had an AE that was considered serious. Serious AEs in the ODN group included pneumonia/UTI, intervertebral disk degeneration, respiratory tract infection, trigger finger, cataract, osteoarthritis, wrist fracture, basal cell carcinoma, colon cancer, and osteoarthritis/abdominal pain; none was considered related to the study drug. Serious AEs in the placebo group included head injuries/syncope, facial palsy/atrial fibrillation/reflux esophagitis, wrist fracture/wound infection, ovarian neoplasm, basal cell carcinoma (2), chronic obstructive pulmonary disease/musculoskeletal chest pain, and abdominal pain/vertigo/dehydration.

Only 18 (9%; 10 placebo, 8 ODN) patients had a laboratory AE; none was reported as serious. Overall, ODN treatment did not result in any clinically important changes in serum calcium level or mineral homeostasis. There were no significant differences between groups in the percentage of patients exceeding predefined limits of change in laboratory values. There were no clinically meaningful changes in patient height, weight, or blood pressure in those who continued ODN treatment for a third year.

A total of 27 patients (14.3%; 15 placebo, 12 ODN) experienced skin-disorder AEs; none was serious, and none of these participants discontinued study therapy. No morphea was observed, and the incidence of cutaneous AEs was similar between treatment groups. There were no discernible patterns with respect to diagnosis, time of onset, or duration across treatment groups.

Eight patients (4.2%; 4 placebo, 4 ODN) discontinued study therapy owing to a clinical AE. Discontinuations were not due to any one particular clinical AE: BMD decrease, fatigue, metastatic colon cancer, and peripheral edema for ODN and gastroesophageal disease, gastric ulcer, and vertebral fracture (2 patients) for placebo. No patients discontinued because of laboratory AEs.

Discussion

Osteoporotic bone loss results from an imbalance in normal bone remodeling favoring bone resorption. During the bone-resorption process, degradation of organic matrix (mostly collagen) is catalyzed by catK, a cysteine protease produced by the osteoclast that is most active under acidic conditions. Inhibition of catK activity would be expected to inhibit this matrix degradation and interfere with bone resorption, and catK inhibitors have been developed and tested as potential therapies to treat osteoporosis.[2–7]

ODN is a selective inhibitor of catK that is effective when administered orally with weekly dosing without regard to food intake. Inhibition of catK enzyme activity by ODN is a reversible process, and other osteoclast activities do not appear to be greatly affected. Preclinical findings in estrogen-deficient nonhuman primates have shown relatively little reduction in bone formation, as well as stimulation of periosteal bone formation,[17] consistent with observations of increased trabecular bone quantity as a result of reduced resorption and a normal formation rate in catK(−/−) mice.[18] Transilial biopsies from a limited subset of the women who completed 2 years of ODN treatment did not show any apparent reduction in activation frequency or bone-formation rate compared with placebo.[16] Thus ODN appears to be relatively "formation sparing." These findings are consistent with ODN having a mechanism of action that differs from that of other antiresorptives, which suppress both bone resorption and formation and which have not been shown to stimulate periosteal bone formation in animal models.

In this extension study, all subjects were rerandomized at the end of the second year to receive either placebo or what is considered to be the most effective dose of ODN, 50 mg, based on year 1 and year 2 data. This rerandomization allowed observation of both the BMD response in those who continued on this dose of ODN and the resolution of effect in those who were switched from active agent to placebo. At the end of 3 years, individuals on the 50-mg dose showed a continued increase in BMD compared with BMD at 2 years at sites of the proximal femur and lumbar spine. The cumulative gains in BMD seen with ODN are similar to those seen with alendronate and zoledronic acid, although BMD increases with ODN did not plateau over time, as has been observed with other antiresorptive therapies.

These results suggest that ODN is effective in achieving improvement in bone density at all measured sites by a reduction in bone resorption, although bone resorption markers are not suppressed to the extent seen in studies of alendronate.[19] Unlike current antiresorptive therapies, which suppress both bone-resorption and bone-formation markers, ODN appeared to suppress bone-formation markers only transiently. Both BSAP and P1NP returned to baseline levels by the end of year 2 despite continued treatment, and both remained at or near baseline during the third year of treatment. TRACP 5b levels indicate that the osteoclasts are still viable and may be involved in signaling even though their resorptive activity has been attenuated, as proposed by Karsdal and colleagues.[20] A further extension of the current study to 5 years is now in progress to monitor additional effects of ODN 50-mg treatment on BMD, bone turnover markers, and safety.

Because ODN does not persist in bone, it is not surprising that after discontinuation of ODN, much of the bone density that had been gained in the initial 2 years was lost during the following year. There was an initial rapid loss in BMD over 6 months, eventually leveling off to near-baseline levels. These data are more similar to the findings with hormone-replacement therapy,[21–24] denosumab,[25] and parathyroid hormone[26] than

with the bisphosphonate group of drugs. This rapid resolution of effect is consistent with the fact that the inhibition of catK by ODN is effectively reversible. This rapid reversibility could be useful if an alteration of the therapeutic approach becomes desirable. On the other hand, maintaining BMD gains requires continuation of therapy.

The biochemical marker data indicate that there is a substantial suppression of bone-resorption markers by ODN at 3 years, with continuing suppression for NTx but partial resolution of effect for CTx and u-DPyr. In contrast to other antiresorptive agents, ODN treatment resulted in little or no persistent inhibition of bone-formation markers by 2 years. The abrupt change in marker levels after discontinuation of treatment, as assessed with s-CTx, may be partly an artefact of samples being analyzed with different assay batches or a biologic response. The marker samples for the first 2 years were assayed in one batch, whereas those from later time points were assayed in a different batch. This likely explains the apparent shift (upward) in biomarker levels observed in all the study groups. For this reason, changes in s-CTx are best estimated by comparison with s-CTx levels in the patients in the placebo/placebo group. Discontinuation of ODN was associated with an increase in markers of bone turnover. The increase in levels of bone-resorption markers was immediate and substantial but transient, largely returning to baseline levels by the end of the third year.

There were no major differences in the incidence of AEs between the two pooled treatment groups, with the exception of cases reported and treated as UTIs/cystitis. Review of the specific events did not reveal any qualitative symptomatic differences from UTIs that are relatively frequent in elderly women. By comparison, the incidence of UTIs was similar across treatment groups in the first 2 years of the study. Only one UTI was confirmed by culture, and none was reported as pyelonephritis. These events resolved without study drug discontinuation, and their clinical significance remains to be seen in the overall clinical program. There were no differences in skin AEs or upper respiratory tract infections between the ODN and placebo groups. The absence of these AEs indicates that the finding of skin adverse effects observed in a clinical study of another catK inhibitor, balicatib, are probably not related directly to inhibition of catK. The present data reflect the high selectivity of ODN for catK, with no significant interaction expected with other cathepsins and no expected mechanism-based off-target effects. Overall, ODN generally was safe and well tolerated.

The data over the first 2 years with the lowest dose of ODN, 3 mg, were particularly interesting in that individuals on this low dose had accelerated bone turnover and BMD results similar to (or, at the distal forearm, slightly worse than) placebo.[16] Thus it is important to note that when these individuals were switched to the 50-mg dose, they had a marked increase in BMD comparable with the effect achieved from initiation with the higher dose from baseline (Supplemental Fig. S1). The lack of benefit from the 3-mg weekly dose may have resulted from insufficiently sustained suppression of catK throughout the duration of the weekly dosing interval. As such, this is a theoretical concern in individuals who are irregularly compliant with the standard dose or who very rapidly metabolize the drug. However, the excellent response in these individuals compared with placebo, that is, treatment-naive subjects, within a year of switching to the effective 50-mg weekly dose is reassuring that the changes are reversible.

In summary, 3 years of ODN treatment increased lumbar spine and proximal femur BMD with a generally favorable safety profile in postmenopausal women with low bone density. Bone-resorption markers were moderately suppressed (except for DPD), whereas bone-formation markers were relatively unaffected in the third year. BMD increases with ODN were substantially reversed within a year of discontinuation. A fracture-prevention study using the 50-mg ODN dose has been initiated to evaluate its efficacy and safety in fracture risk reduction in postmenopausal women with osteoporosis.

Disclosures

JAE, 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 meet the International Committee of Medical Journal Editors (ICMJE) 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.

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 saw and approved the final version. JAE has served as a scientific advisor or consultant to Amgen, deCode, Lilly, Merck, Novartis, Roche-GSK, sanofi-aventis, Servier and Wyeth Australia and has received research support from Amgen, GE-Lunar, Lilly, Merck, Novartis, Roche-GSK, sanofi-aventis, and Servier.

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

DJH participated in the study, collected the data, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and saw and approved the final version. DJH has received consulting, advisory board, or lectures fees and research support from Amgen, Merck (MSD), Novartis, and Nycomed.

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 saw and approved the final version. MRM has served as a scientific advisor to and received research funding from Amgen, Lilly, Merck, Novartis, Procter & Gamble, and sanofi-aventis.

IRR participated in the study, collected and assembled the data, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and saw and approved the final version. IRR has received consultant, speaker,

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RR participated in the study, collected and assembled the data, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and saw and approved the final version. RR has served as a scientific advisor and received research support from Merck (MSD), Novartis, Servier, Danone.

HR participated in the study, collected and assembled the data, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and saw and approved the final version. HR has been a paid consultant for Lilly, Amgen, Roche, Novartis, Nycomed, and Servier; a paid speaker for Merck (MSD), Lilly, Servier, Roche, and Nycomed; and has received grant/research support from Lilly and Roche.

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 saw and approved the final version. NV is an employee of Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who may 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 saw and approved the final version. CMH is an employee of Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who owns stock and/or holds 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 saw and approved the final version. CDS is an employee of Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who may own stock and/or hold stock options in the company.

RP assembled the data, performed analyses, interpreted the results, provided substantive suggestions for revision on iterations of the draft manuscript, and saw and approved the final version. RP is an employee of Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who may 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 saw and approved the final version. ACS is an employee of Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who owns stock and holds stock options in the company.

BAI 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 saw and approved the final version. BAI is an employee of Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who may own stock and/or hold stock options in the company.

AL 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 saw and approved the final version. AL is employee of Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., who may own stock and/or hold stock options in the company.

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