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Comparison of the Effect of Denosumab and Alendronate on BMD and Biochemical Markers of Bone Turnover in Postmenopausal Women With Low Bone Mass: A Randomized, Blinded, Phase 3 Trial*

Jacques P Brown,[1] Richard L Prince,[2] Chad Deal,[3] Robert R Recker,[4] Douglas P Kiel,[5] Luiz H de Gregorio,[6] Peyman Hadji,[7] Lorenz C Hofbauer,[8] Jose M Álvaro-Gracia,[9] Huei Wang,[10] Matthew Austin,[10] Rachel B Wagman,[11,12] Richard Newmark,[10] Cesar Libanati,[10] Javier San Martin,[10] and Henry G Bone[13]

ABSTRACT: Denosumab is a fully human monoclonal antibody that inhibits bone resorption by neutralizing RANKL, a key mediator of osteoclast formation, function, and survival. This phase 3, multicenter, double-blind study compared the efficacy and safety of denosumab with alendronate in postmenopausal women with low bone mass. One thousand one hundred eighty-nine postmenopausal women with a T-score ≤ -2.0 at the lumbar spine or total hip were randomized 1:1 to receive subcutaneous denosumab injections (60 mg every 6 mo [Q6M]) plus oral placebo weekly ($n = 594$) or oral alendronate weekly (70 mg) plus subcutaneous placebo injections Q6M ($n = 595$). Changes in BMD were assessed at the total hip, femoral neck, trochanter, lumbar spine, and one-third radius at 6 and 12 mo and in bone turnover markers at months 1, 3, 6, 9, and 12. Safety was evaluated by monitoring adverse events and laboratory values. At the total hip, denosumab significantly increased BMD compared with alendronate at month 12 (3.5% versus 2.6%; $p < 0.0001$). Furthermore, significantly greater increases in BMD were observed with denosumab treatment at all measured skeletal sites (12-mo treatment difference: 0.6%, femoral neck; 1.0%, trochanter; 1.1%, lumbar spine; 0.6%, one-third radius; $p \leq 0.0002$ all sites). Denosumab treatment led to significantly greater reduction of bone turnover markers compared with alendronate therapy. Adverse events and laboratory values were similar for denosumab- and alendronate-treated subjects. Denosumab showed significantly larger gains in BMD and greater reduction in bone turnover markers compared with alendronate. The overall safety profile was similar for both treatments.
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Key words: BMD, denosumab, alendronate, postmenopausal osteoporosis, biochemical markers of bone turnover

INTRODUCTION

Postmenopausal osteoporosis is a disease characterized by decreased bone mass, microarchitectural deterioration of the skeleton, and impaired bone strength.[1] The therapeutic objective of treatment is to alter the balance of bone remodeling to increase bone mass. Antiresorptive agents are the predominant therapeutic category

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[1]Laval University and Le Centre Hospitalier Universitaire de Québec, Quebec City, Québec, Canada; [2]Sir Charles Gairdner Hospital, University of Western Australia, Perth, Australia; [3]Cleveland Clinic, Cleveland, Ohio, USA; [4]Creighton University, Omaha, Nebraska, USA; [5]Institute for Aging Research, Hebrew SeniorLife and Harvard Medical School, Boston, Massachusetts, USA; [6]SYNARC/CCBR, Rio de Janeiro, Brazil; [7]Philipps-University of Marburg, Marburg, Germany; [8]Department of Medicine III, Technical University, Dresden, Germany; [9]Hospital de la Princesa, Madrid, Spain; [10]Amgen, Thousand Oaks, California, USA; [11]Amgen, San Francisco, California, USA; [12]Stanford University School of Medicine, Stanford, California, USA; [13]Michigan Bone and Mineral Clinic, Detroit, Michigan, USA.

for the prevention and treatment of bone loss, and the nitrogen-containing bisphosphonates are the most commonly used.[2–4] These drugs significantly reduce bone turnover by binding to the mineralized surface of bone and inhibiting the bone-resorbing activity of mature osteoclasts. This results in an increase in BMD and reduction in risk for fracture.[5–13]

Denosumab is a novel antiresorptive agent in late-stage clinical development that also inhibits osteoclast-mediated bone resorption but works through a different pathway than bisphosphonates. Denosumab binds with high affinity and specificity to RANKL, a key mediator of osteoclast differentiation, function, and survival.[14–16] In published phase 2 and 3 studies that evaluated the effect of denosumab in postmenopausal women with low bone mass, denosumab treatment inhibited bone resorption and remodeling as measured by decreases in biochemical markers of bone turnover and increases in BMD at all measured skeletal sites.[17–20]

The different mechanisms by which denosumab and alendronate inhibit bone resorption serve to raise the question as to how these agents compare with respect to efficacy measurements and safety profiles. Here, we describe results from a phase 3 randomized, double-blind study designed to evaluate efficacy and safety of the proposed therapeutic dose of denosumab (60 mg subcutaneously every 6 mo) with alendronate (70 mg orally every week) through 12 mo of treatment in postmenopausal women with low bone mass.

MATERIALS AND METHODS

Subject eligibility

Ambulatory postmenopausal women in general good health and with a T-score ≤ -2.0 at the proximal femur ("total hip") or lumbar spine by DXA were eligible. Subjects were required to have at least one hip and at least two vertebrae (L_1–L_4) that were evaluable by DXA. Additional exclusion criteria included prior administration of intravenous bisphosphonates, fluoride (except for dental treatment) or strontium; use of drugs with known bone activity within 3 mo of randomization; current enrollment in or <1 mo since completion of other drug trials; evidence of an active disease known to affect bone metabolism; malignancy within the past 5 yr (except basal or squamous cell carcinoma or cervical or breast cancer in situ); impaired renal function; or contraindications for alendronate therapy. Subjects with screening serum 25-hydroxyvitamin D [25(OH)D] concentrations <12 ng/ml were ineligible but could undergo vitamin D repletion with ergocalciferol for 2 wk and be rescreened.

The study was approved by the Institutional Review Board or Ethics Committee at each study site and was conducted in accordance with appropriate country regulations and the International Conference on Harmonisation Good Clinical Practice guidelines. Subjects provided written informed consent before enrollment.

Study design

The Determining Efficacy: Comparison of Initiating Denosumab versus Alendronate (DECIDE) trial was a phase 3 randomized, double-blind, double-dummy, active-controlled, parallel-group, international, multicenter, noninferiority study. Enrollment occurred at 86 sites in Western Europe, North and South America, and Australia. Subjects were randomized 1:1 to receive a 1 ml subcutaneous injection of denosumab (60 mg) every 6 mo (Q6M) plus an oral placebo tablet once weekly or a 1-ml placebo injection Q6M plus oral branded alendronate (70 mg; Fosamax; Merck) weekly. The randomization schedule was prepared by the study sponsor before trial initiation and was based on randomly permuted blocks. The denosumab solution contained 60 mg/ml denosumab, 5% sorbitol, and 10 mM sodium acetate in Water for Injection (USP), pH 5.2. Except for the protein content, the placebo injection solution was identical to the denosumab injection solution. All subjects were instructed to take supplements of $\geq$500 mg calcium daily. Daily vitamin D supplementation was determined according to baseline serum 25(OH)D concentration. The dosage of vitamin D was either $\geq$400 IU vitamin D daily if screening 25(OH)D was >20 ng/ml or $\geq$800 IU vitamin D daily if screening 25(OH)D was $\geq$12 to $\leq$20 ng/ml. The primary endpoint for this study was percent change from baseline of the total hip BMD at month 12 in subjects treated with denosumab versus alendronate. Key secondary endpoints included the percent change from baseline in BMD at the femoral neck, trochanter, lumbar spine, and one-third radius at month 12. Additional endpoints included percent change in serum C-telopeptide (sCTX1) and intact N-terminal propeptide of type 1 procollagen (P1NP) from baseline at months 1, 3, 6, 9, and 12.

Study procedures

After screening (which served as the baseline laboratory and radiology assessments if the subject enrolled), study visits were scheduled to occur on study day 1 (randomization) and months 1, 3, 6, 9, and 12. A physical examination was completed at baseline and month 12. Vital signs were recorded at baseline and months 6 and 12. Concomitant medications were recorded at all study visits. BMD at the total hip, lumbar spine, and forearm at baseline and at months 6 and 12 were measured by DXA (Hologic or GE Lunar). DXA scans were performed in duplicate at baseline and month 12 to reduce measurement error and machine variance. Overnight fasting serum samples were collected for measurement of sCTX1 (Serum Crosslaps ELISA; Nordic Biosciences) and P1NP (UniQ P1NP RIA; Orion Diagnostica Oy) at all study visits and were batch tested. Hematology assessments and serum chemistries were recorded at baseline and at months 1, 6, and 12. Serum was collected for detection of anti-denosumab antibodies at study day 1 and month 12. The strategy for testing for anti-denosumab antibodies involved two serial assays. First, a validated electrochemiluminescent immunoassay was used to detect binding antibodies to denosumab. Reactive samples were subsequently tested for neutralizing activity in a cell-based assay.[21] Safety was monitored by recording adverse events and evaluating serum chemistry and hematology values. Site investigators classified adverse events as treatment related if they considered the event to be possibly or probably

related to the study treatment, without unblinding of the treatment assignment. Oral tablets (alendronate or placebo) were dispensed at study day 1 and months 3, 6, and 9. Oral tablet accountability was done at the month 3, 6, 9, and 12 visits. Injections (denosumab or placebo) were administered at study day 1 and month 6 after all study-related procedures for each visit were completed.

Statistical methods

The primary hypothesis was that treatment with denosumab would be noninferior to treatment with alendronate with respect to the mean percent change in the total hip BMD at month 12. Secondary hypotheses included superiority at the total hip and one-third radius and noninferiority at the trochanter, femoral neck, and lumbar spine with respect to the mean percent change in BMD at month 12. A sample size of 550 subjects per group, assuming a 10% drop-out rate through month 12, was estimated to provide at least 96% power for the primary endpoint.

The noninferiority margins for the difference of percent change from baseline in BMD between the treatment groups were based on results from randomized controlled clinical trials comparing alendronate (10 mg daily or 70 mg weekly) with placebo in postmenopausal women with a follow-up period of at least 1 yr and reported total hip BMD data at 1 yr.[22–24] To evaluate whether denosumab retained at least 50% of treatment effect of alendronate at each skeletal site, noninferiority margins were calculated as 50% of the lower bounds of the 95% CIs for the treatment differences (alendronate–placebo), which were based on the meta-analysis from random effect models. The noninferiority margins for the difference of percent change from baseline in BMD between the treatment groups were –1.22% for the total hip, –2.29% for the lumbar spine, –1.04% for the femoral neck, and –1.65% for the trochanter.

A sequential test procedure was used to control the type 1 error rate at 5% for the primary and secondary hypotheses. Secondary multiplicity adjustments[25] also were applied separately in sCTX1 and P1NP analyses to control the endpoint-specific type 1 error rates at 5% because of testing at multiple time points. The secondary adjustments were applied independently of controlling the overall error rate for primary and secondary efficacy endpoints.

The primary and secondary efficacy analyses included all randomized subjects with a baseline measurement and at least one postbaseline measurement at or before the month 12 time point. Missing data were imputed using the last observation carried forward (LOCF) method. A per protocol analysis for the primary and secondary efficacy endpoints also were performed to assess the robustness of the primary analyses. Analyses of changes in bone turnover markers included all randomized subjects with a measurement at baseline at the time point of interest with no imputation for missing data. Safety analyses included all randomized subjects who received at least one dose of active study medication.

The analysis of the percent change in BMD at each skeletal site was performed using an analysis of covariance (ANCOVA) model with treatment, baseline BMD value, instrument manufacturer, and the interaction of baseline BMD and instrument manufacturer as fixed effects. For analysis, the average of the duplicate BMD measurements was used. The primary results were based on the point estimate for the least-squares mean and the two-sided 95% CI for the treatment difference at the 12-mo time point, and the results were rounded to one decimal place. The proportion of patients with BMD gains >0% was also compared between treatment groups at all skeletal sites. In addition, comparisons of the proportion of subjects achieving the least significant change (LSC) in BMD were made between treatment groups at all skeletal sites measured. The LSC was calculated using the duplicate scans at baseline for each measured skeletal site based on the precision of the DXA measurements using the root mean square CV (%CV) multiplied by 2.77.[26] This value is expressed as %CV rather than the absolute value to account for more than one manufacturer of densitometry equipment being used. Additional analyses, using the LSC expressed as an absolute value, were performed to assess the robustness of the responder analyses.

Changes in levels of biochemical markers of bone turnover exhibited a nonsymmetric distribution and thus were summarized using medians. Values falling below the quantifiable limit were set to the lower limit for the assay as defined by the manufacturer. Differences in percent change in bone turnover markers between treatment groups were analyzed using the Wilcoxon rank-sum test. Comparisons between the denosumab and alendronate groups with regard to safety are descriptive and unadjusted for multiple comparisons; p values are based on Fisher's exact test.

The study sponsor was responsible for the study design, conduct, data collection, and statistical analysis. Authors had access to all data and were responsible for acquisition and interpretation of the data, drafting and/or revising the manuscript for intellectual content, and the decision to submit for publication. Medical writing assistance was provided by the sponsor.

RESULTS

Study participants

Data were collected from April 2006 to December 2007. In total, 1189 subjects were randomized: 594 received denosumab injection plus oral placebo and 595 received placebo injection plus oral alendronate (Fig. 1). Subjects were considered to be treatment compliant if they received all injections and took ≥80% of the oral tablets. Similar proportions of subjects in each group were treatment compliant (93% denosumab, 91% alendronate). Most subjects (94%) completed 12 mo of study. The reasons for discontinuation were similar between the treatment groups, with withdrawal of consent being the most common.

Baseline demographics and characteristics were balanced between the treatment groups (Table 1). A previous fracture was reported by 49% of denosumab subjects and 51% of alendronate subjects; of these, 40% and 41% were classified as osteoporotic fractures for denosumab- and alendronate-treated subjects, respectively. Nearly one quarter

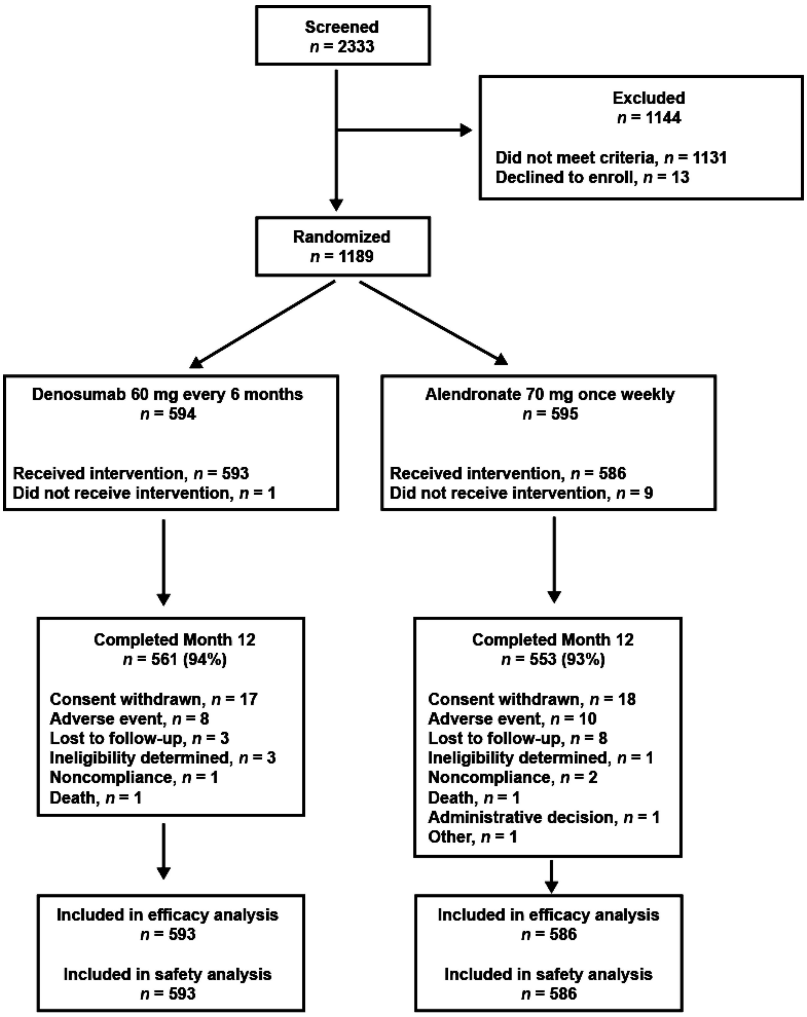

FIG. 1. Subject disposition at month 12.

(23% denosumab; 24% alendronate) of subjects reported prior use of osteoporosis medications. An oral bisphosphonate had been used by 13% of denosumab subjects and 11% of alendronate subjects. The median (Q1, Q3) time of prior oral bisphosphonate use was similar for both the denosumab (8.0 [2.0, 17.5] mo) and alendronate (6.0 [1.3, 13.0] mo) groups. The median time between discontinuation of prior bisphosphonate therapy and enrollment in the study was 32.9 mo (24.5, 39.0) for the denosumab group and 25.9 mo (14.0, 38.0) for the alendronate group.

Efficacy

BMD: The mean percent change from baseline in BMD at the total hip was 3.5% for denosumab-treated subjects and 2.6% for alendronate-treated subjects (one-sided $p < 0.0001$), for a treatment difference (least squares mean [95% CI]) of 1.0% [0.7–1.2] at month 12, excluding the predefined noninferiority margin of –1.22% (Fig. 2). Because noninferiority for the primary efficacy endpoint was met, the secondary endpoints were inferentially evaluated. Prespecified superiority testing showed significantly greater increases in BMD in subjects treated with denosumab compared with subjects treated with alendronate at the total hip, trochanter (4.5% versus 3.4%, $p < 0.0001$) and one-third radius (1.1% versus 0.6%; $p = 0.0001$; Supplementary Fig. 1). Because the noninferiority hypotheses at the femoral neck and lumbar spine were achieved, additional analyses of superiority testing at the femoral neck and lumbar spine were performed. Superiority testing at the femoral neck (2.4% versus 1.8%; $p = 0.0001$) and lumbar spine (5.3% versus 4.2%; $p < 0.0001$) also showed greater gains in BMD for denosumab- versus alendronate-treated subjects (Fig. 3). Results of analyses using intent-to-treat and per protocol populations were consistent. Additionally, BMD gains at all evaluated skeletal sites were significantly greater for the denosumab group at month 6 ($p \leq 0.0014$), the earliest time point measured (Fig. 3 and Suppl. Fig. 1).

Most subjects in both treatment groups either maintained or gained BMD at the total hip and lumbar spine at month 12. Because duplicate baseline DXA measurements were performed in this study, the LSC at each skeletal site could be calculated. The LSC was calculated as 2.76% at the total hip and 3.66% at the lumbar spine. A significantly greater percent of denosumab subjects had an increase in BMD greater than the calculated LSC at the total hip (65% versus 44%; $p < 0.0001$) and lumbar spine (71% versus 56%; $p <$

TABLE 1. BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

	Denosumab 60 mg Q6M (N = 594)	*Alendronate 70 mg QW (N = 595)*
Age (yr) [mean (SD)]	64.1 (8.6)	64.6 (8.3)
Ethnic group/race [*n* (%)]		
White	502 (85)	502 (84)
Hispanic or Latino	66 (11)	69 (12)
Black	7 (1)	9 (2)
Other*	19 (3)	15 (3)
Geographic location [*n* (%)]		
North America	330 (56)	332 (56)
Europe	161 (27)	154 (26)
South America	87 (15)	88 (14)
Australia	16 (3)	21 (4)
Years since menopause [mean (SD)]	16.5 (10.2)	17.8 (9.8)
Baseline BMD T-score [mean (SD)]		
Total hip	–1.75 (0.79)	–1.69 (0.81)
Lumbar spine	–2.57 (0.75)	–2.57 (0.75)
Baseline BTM levels [mean (SD)]		
sCTX1 (ng/ml)	0.705 (0.312)	0.654 (0.294)
P1NP (μg/liter)	54.17 (21.36)	50.50 (22.23)
25(OH)vitamin D (ng/ml) [mean (SD)]	29.1 (12.9)	29.1 (13.5)

* Includes patients who self-identified as Asian, Japanese, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, or Other.

BTM, bone turnover markers; SCTX1, serum C-telopeptide; P1NP, intact N-terminal propeptide of type 1 procollagen.

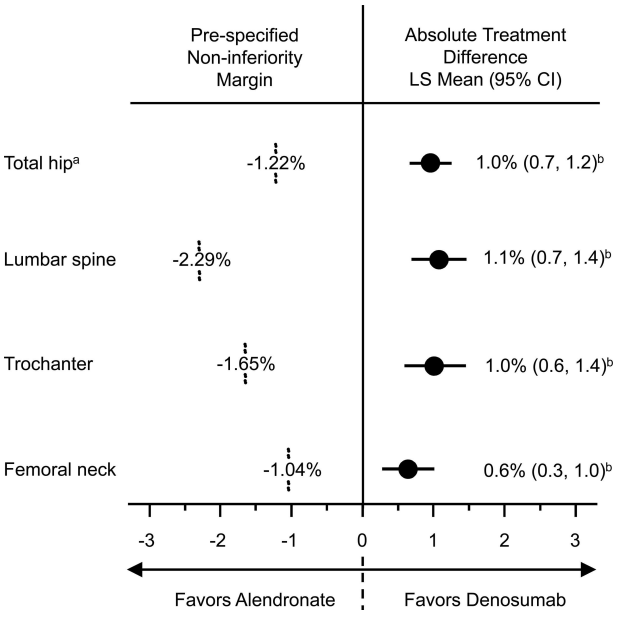

FIG. 2. Prespecified noninferiority margins for the total hip, femoral neck, trochanter, and lumbar spine are indicated on the left. The one-third radius was tested for superiority only; thus, a noninferiority margin was not prespecified for this skeletal site. The least squares mean (95% CI) treatment difference between the denosumab and alendronate groups are shown on the right; treatment differences were rounded to one decimal place; ([a]primary hypothesis; [b]significantly different from alendronate, $p \leq 0.0001$).

0.0001) than alendronate subjects. Results from analyses using LSC expressed as absolute values were consistent. More denosumab than alendronate subjects gained BMD (>0%) at the femoral neck, trochanter, and one-third radius ($p < 0.05$ for all sites; data not shown).

Bone turnover markers: Biochemical markers of bone turnover were reduced in both the denosumab and alendronate groups (Fig. 4). In denosumab-treated subjects, sCTX1 reduction was rapid, with maximal median decreases from baseline observed at month 1 (–89%; Fig. 4) and was significantly greater than that observed for alendronate-treated subjects (–61%; $p < 0.0001$). Similarly, at month 3, median decreases were greater in the denosumab group than the alendronate group (–89% versus –66%, respectively; $p < 0.0001$). At month 6, the end of the dosing interval for denosumab, the median sCTX1 reductions approached that of the alendronate group (–77% versus –73%, respectively), although the treatment difference remained significant ($p = 0.0001$). At month 9, 3 mo after subjects received the second dose of denosumab, a decrease in sCTX1 was again observed for the denosumab group (–89% versus –76% for the alendronate group; $p < 0.0001$). At month 12, the median decreases in sCTX1 were similar for both treatment groups (–74% denosumab, –76% alendronate; $p = 0.52$).

Decreases in the bone formation marker P1NP also were noted in both treatment groups. Denosumab-treated subjects had significantly greater decreases in serum concentrations of P1NP than alendronate-treated subjects at each time point assessed ($p < 0.0001$; Fig. 4B). At month 1, P1NP levels decreased from baseline to –26% in the denosumab group and –11% in the alendronate group. Maximal reduction in P1NP was observed in the denosumab group by month 3 (–76% versus –56% for alendronate) and was maintained through month 12 (–72% versus –65% for alendronate; Fig. 4B). For the alendronate group, the maximal decrease in P1NP was observed at month 9 (–65% alendronate versus –78% for denosumab).

Safety

Adverse events: No significant difference was observed in the overall incidence of adverse events between denosumab- and alendronate-treated subjects (80.9% versus 82.3%; $p = 0.60$; Table 2), including adverse events of gastrointestinal disorders, infections, and neoplasms. Most adverse events were considered mild or moderate in severity. Adverse events considered by the investigator to be related to treatment were reported for a similar percent of subjects in the denosumab (17.0%) and alendronate (18.3%) groups. Serious adverse event (SAE) incidence was similar between denosumab-treated subjects ($n = 34$ [5.7%]) and alendronate-treated subjects ($n = 37$ [6.3%]). Two SAEs (one vaginal neoplasm and one severe arthralgia, both in the alendronate group) were assessed by investigators to be possibly or probably related to treatment (Table 2). The proportion of adverse events leading to discontinuation of investigational product or study withdrawal was small and

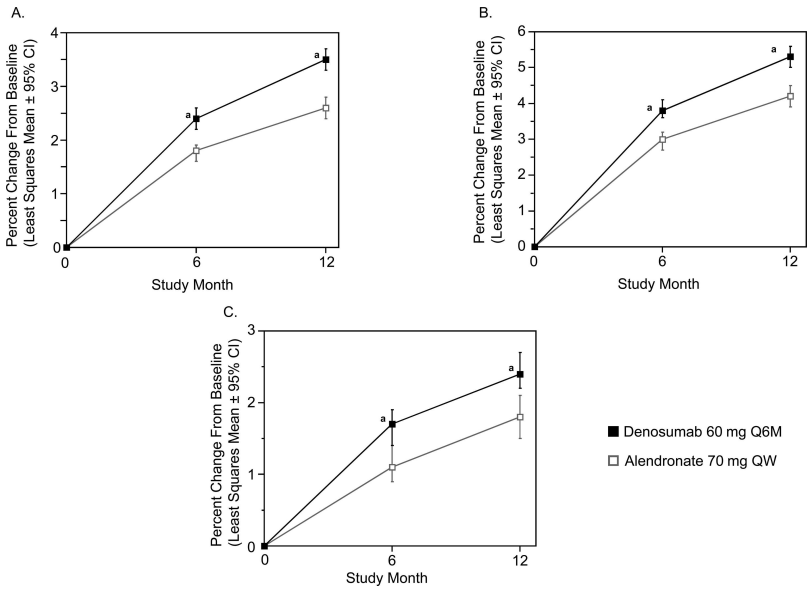

FIG. 3. Least squares mean (95% CI) percent change from baseline at months 6 and 12 in BMD at the (A) total hip, (B) lumbar spine, and (C) femoral neck in denosumab and alendronate groups ([a]significantly different from alendronate, $p \leq 0.0014$).

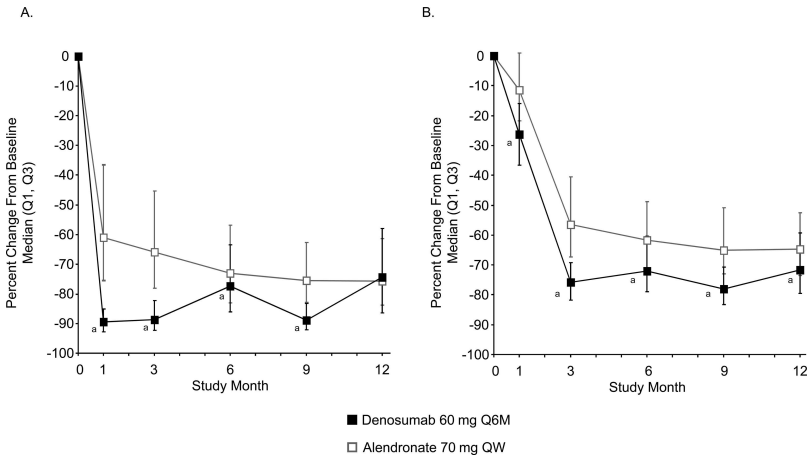

FIG. 4. Median (Q1, Q3) percent change from baseline in the bone turnover markers (A) sCTX1 and (B) P1NP through month 12 ([a]significantly different from alendronate, $p \leq 0.0001$).

similar between groups (Table 2). Two deaths occurred during the study and were not considered to be related to either investigational product by investigators. One denosumab-treated subject died of cardio-respiratory arrest and one alendronate-treated subject died of a metastatic neoplasm of unknown origin.

The incidence and types of infections were similar between the treatment groups (221 [37.3%] denosumab; 207 [35.3%] alendronate). Nasopharyngitis (7.6% denosumab; 7.3% alendronate), influenza (6.9% denosumab; 7.2% alendronate), upper respiratory tract infection (6.1% denosumab; 4.4% alendronate), bronchitis (3.2% denosumab; 3.6% alendronate), and urinary tract infection (3.0% denosumab; 2.9% alendronate) were the most commonly reported infections. SAEs of infection were balanced between treatment groups, with nine (1.5%) and six (1.0%) reports for denosumab and alendronate-treated subjects, respectively. Diverticulitis (three denosumab; zero alendronate) and pneumonia (one denosumab; three alendronate) were the most common serious infections reported (Table 3).

Benign or malignant cysts or neoplasms were reported for similar numbers of subjects in each group (Table 2). Malignant neoplasms were reported for six (1.0%) denosumab and five (0.9%) alendronate subjects. There was no significant pattern or difference in the type or occurrence of serious malignancies in either treatment group (Table 3). Neoplasms not classified as SAEs were benign, dermatologic, or not otherwise specified. Benign neoplasms of the breast (0.3% denosumab; 0% alendronate), kidney (0.3% denosumab; 0% alendronate), and thyroid gland (0.2% denosumab; 0.3% alendronate) were most frequently reported.

This study was not powered to compare fracture rates between treatment groups, but fractures were reported as adverse events (Table 2) and were not adjudicated. Overall, similar numbers of subjects in each treatment group reported at least one on-study fracture (24 [4.0%] denosumab; 19 [3.2%] alendronate).

Laboratory values: At month 1, there was a decrease in albumin-adjusted serum calcium concentrations in the denosumab group compared with the alendronate group

Table 2. Adverse Events Summary

	Denosumab 60 mg Q6M (N = 593)	*Alendronate 70 mg QW (N = 586)*	*p**
All adverse events	480 (80.9)	482 (82.3)	0.60
Treatment-related	101 (17.0)	107 (8.3)	0.59
Leading to study withdrawal	8 (1.3)	10 (1.7)	0.64
Fatal	1 (0.2)	1 (0.2)	1.0
Serious adverse events	34 (5.7)	37 (6.3)	0.71
Treatment-related	0 (0)	2 (0.3)	0.25
Leading to study withdrawal	3 (0.5)	4 (0.7)	0.72
Adverse event occurring with >10% frequency			
Arthralgia	75 (12.6)	56 (9.6)	0.10
Adverse events of interest			
Gastrointestinal disorders	164 (27.7)	168 (28.7)	0.75
Infections	221 (37.3)	207 (35.3)	0.51
Neoplasms (benign or malignant)	21 (3.5)	15 (2.6)	0.40
All fractures	24 (4.0)	19 (3.2)	0.54
Osteoporotic fractures†	18 (3.0)	13 (2.2)	0.37

Values reported are *n* (%).
* Based on Fisher's exact test.
† Excludes fractures of the face, hands, or feet, or those caused by severe trauma.

Table 3. Serious Adverse Events of Infection or Malignancy

	Denosumab 60 mg Q6M (N = 593)	*Alendronate 70 mg QW (N = 586)*	*p**
Subjects with reported SAEs of infections	9 (1.5)	6 (1.0)	0.61
Diverticulitis	3 (0.5)	0 (0.0)	0.25
Ear infection	1 (0.2)	0 (0.0)	1.00
Localized infection (finger)	1 (0.2)	0 (0.0)	1.00
Pneumonia	1 (0.2)	3 (0.5)	0.37
Pseudomembranous colitis†	1 (0.2)	0 (0.0)	1.00
Pyelonephritis	1 (0.2)	0 (0.0)	1.00
Sepsis	1 (0.2)	0 (0.0)	1.00
Urosepsis	1 (0.2)	0 (0.0)	1.00
Abscessed limb	0 (0.0)	1 (0.2)	0.50
Infected cyst	0 (0.0)	1 (0.2)	0.50
Upper respiratory tract infection	0 (0.0)	1 (0.2)	0.50
Subjects with reported SAEs of malignant neoplasm	6 (1.0)	5 (0.9)	1.00
Breast cancer	2 (0.3)	1 (0.2)	1.00
Gastric cancer‡	1 (0.2)	0 (0.0)	1.00
Metastases to liver‡	1 (0.2)	0 (0.0)	1.00
Mycosis fungoides	1 (0.2)	0 (0.0)	1.00
Renal cell carcinoma stage unspecified	1 (0.2)	0 (0.0)	1.00
Squamous cell carcinoma	1 (0.2)	0 (0.0)	1.00
Metastatic neoplasm	0 (0.0)	1 (0.2)	0.50
Ovarian cancer recurrent	0 (0.0)	1 (0.2)	0.50
Small cell lung cancer metastatic	0 (0.0)	1 (0.2)	0.50
Vaginal cancer	0 (0.0)	1 (0.2)	0.50

Values reported are *n* (%).
* Based on Fisher's exact test.
† Reported for one subject with diverticulitis.
‡ Reported for the same subject.

(mean change: –2.36% versus –0.88%). At months 6 and 12, the mean percent changes in serum calcium levels were similar for each group (data not shown). There were no reports of symptomatic hypocalcemia. One denosumab-treated subject developed an asymptomatic grade 2 decrease in albumin-adjusted serum calcium concentrations (calcium concentration < 8.0–7.0 mg/dl; Common Terminology Criteria for Adverse Events v3.0) at month 1 (7.0 mg/dl), but calcium concentrations spontaneously returned to values within the normal range by the next time point evaluated. At baseline, no subjects tested positive for anti-denosumab antibodies, and no denosumab-treated subjects (592 tested) developed antibodies to denosumab during the course of this study.

DISCUSSION

In this study, the efficacy and safety of denosumab (60 mg SC Q6M) was compared with that of the widely used antiresorptive therapy, alendronate (70 mg oral QW), by assessment of BMD and bone turnover markers in postmenopausal women with low bone mass. Treatment with denosumab resulted in greater increases in BMD at the total hip, lumbar spine, femoral neck, trochanter, and one-third radius than with alendronate therapy. In addition, higher proportions of subjects treated with denosumab, compared with alendronate, experienced changes in BMD >0% and greater than the calculated LSC at the total hip and lumbar spine at all postbaseline assessments. The safety profile of these agents was similar and both appeared to be well tolerated by subjects in this study.

Compared with alendronate, treatment with denosumab resulted in significantly greater decreases in biochemical markers of bone turnover sCTX1 and P1NP at each time point assessed through month 9 for sCTX1 and month 12 for P1NP. The sCTX1 inhibition profile over time differed between the two agents. Maximum reduction of sCTX1 in the alendronate group was reached at month 3 and remained constant throughout the study. In contrast, maximal reduction of sCTX1 in the denosumab group was observed at month 1, the earliest time point measured, with attenuated reduction in sCTX1 at the end of the Q6M dosing interval. Differences in the level and pattern of sCTX1 decreases may reflect the distinct mechanisms by which denosumab and alendronate inhibit bone resorption. Bisphosphonates have high affinity for hydroxyapatite and incorporate into the bone matrix, bringing these agents in close proximity to osteoclasts.[27] In contrast, denosumab binds with high affinity and specificity to RANKL, a key mediator of osteoclast differentiation, function, and survival.[14,15] The attenuation of the effect of denosumab on reduction in bone turnover marker levels seems to be associated with recovery of bone turnover, something that has

not been observed with bisphosphonate treatment. Evaluation of the bone formation marker, P1NP, showed a time delay in reduction relative to sCTX1 with both treatments, showing that bone remodeling remained coupled with both denosumab and alendronate therapy.

To our knowledge, this study is the first published report of an antiresorptive agent, denosumab, that achieved significantly greater gains in BMD at all measured skeletal sites when directly compared with alendronate. In contrast, previously published head-to-head studies comparing alendronate with other weekly or monthly bisphosphonates in postmenopausal women with low bone mass showed that alendronate-treated subjects had greater gains in BMD than those treated with risedronate or ibandronate.[28–30] Although denosumab and alendronate increase BMD by decreasing osteoclastic bone resorption, the mechanism of action and pharmacodynamic profiles of these agents are different. We hypothesize that the greater effect of denosumab versus alendronate on BMD at the skeletal sites measured in this study, as well as the rapid reduction in bone turnover, may be related to its ability as a monoclonal antibody to RANKL to inhibit osteoclast development and activity.

The safety profiles were similar between subjects treated with denosumab and alendronate. Most reported adverse events were generally mild to moderate in severity, and there was no apparent temporal relationship between the reported adverse events and administration of investigational product. The overall rates of adverse events and SAEs of infection and neoplasm were balanced between the denosumab and alendronate groups, with no discernible pattern of differences between treatment groups in the type or incidence of infections or neoplasms. There is interest in the rate of infection and neoplasm with denosumab treatment because RANKL and RANK also are expressed on cells of the immune system, as well as precursor and mature osteoclasts and osteoblasts. Results from preclinical[31] and clinical[32] studies suggest that the RANKL/RANK pathway does not have an essential role in the adult immune system. The results of this trial are consistent with findings from those earlier studies.

In summary, results from this head-to-head blinded study in postmenopausal women with low bone mass provide evidence that denosumab treatment produced both significantly more reduction in bone resorption and greater gains in BMD at all measured skeletal sites compared with alendronate. The frequency and pattern of reported adverse events was similar between the two agents. The effect of denosumab on reduction of fractures is under evaluation in postmenopausal women with osteoporosis in a separate clinical trial.

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Address reprint requests to:
Jacques P Brown, MD
Centre de Recherche du CHUL
Room S-784, 2705 Laurier Boulevard
Quebec City, PQ G1V 4G2, Canada
E-mail: jacques.brown@crchul.ulaval.ca

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APPENDIX: LIST OF DECIDE STUDY INVESTIGATORS

Argentina	Dr Carlos Alfredo Mautalen, Dr Jose Zanchetta
Australia	Dr Richard Prince, Dr John Eisman, Dr Anthony Roberts, Dr Susan Davis
Belgium	Dr Jean-Yves Reginster, Dr Jean-Marc Kaufman, Dr Jean-Pierre Devogelaer, Dr Steven Boonen
Brazil	Dr Luiz Henrique de Gregorio, Dr Cristiano A.F. Zerbini
Canada	Dr Jacques Brown, Dr David Kendler, Dr Chui Kin Yuen, Dr Wojciech Olszynski, Dr Robert Josse, Dr Angela Cheung, Dr Majed Khraishi
Denmark	Dr Hans Chr Hoeck, Dr Christence Teglbjærg, Dr Peter Alexandersen, Dr Jens-Erik Beck Jensen
Germany	Dr Johannes Pfeilschifter, Dr Peyman Hadji, Dr Reiner Bartl, Dr Johann Ringe, Dr Jutta Semler
Spain	Dr Jose Maria Alvaro-Gracia, Dr Ramón Pérez Cano, Dr Aldolfo Díez-Perez, Dr Manuel Diaz Curiel, Dr Jorge Cannata-Andía
United Kingdom	Dr Thomas Sheeran, Dr Jonathan Reeves, Dr David M Reid, Dr David Hosking
United States	Dr Michael Bolognese, Dr Molly Omizo, Dr Chris Recknor, Dr Henry Bone, Dr Robert Recker, Dr Eric Lee, Dr Maria Greenwald, Dr Alfred Moffett, Jr., Dr Paul Miller, Dr Gurmej Dhillon, Dr Alan Kivitz, Dr Keith Aqua, Dr Wayne Larson, Dr Munro Peacock, Dr Roberto Civitelli, Dr Clifford Rosen, Dr Francis Burch, Dr Robert Trapp, Dr Joseph Tucci, Dr Howard Knapp, Dr Laura Marchiando, Dr Sydney Bonnick, Dr Melvin Stjernholm, Dr Susan Greenspan, Dr Chad Deal, Dr Robert G. Feldman, Dr Michael Maricic, Dr Mark Iannini, Dr Steven Klein, Dr Kenneth Saag, Dr Eric Orwoll, Dr Douglas Kiel, Dr Stanley Cohen, Dr Dennis Linden, Dr Fergus McKiernan, Dr Anthony Sebba, Dr Felicia Cosman, Dr John Aloia, Dr Robert Downs, Dr Elizabeth Barrett–Connor, Dr Gary Feldman, Dr Don Wheeler, Dr Bonnie Shanis, Dr Leland Graves, Dr Stuart Silverman, Dr William Shergy, Dr Alan Brodsky, Dr G. Raychael Gonzales, Dr Diana Antoniucci