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ORIGINAL ARTICLE

Adherence, preference, and satisfaction of postmenopausal women taking denosumab or alendronate

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Abstract
Summary In this study, 250 women with osteoporosis were randomized to 12 months with subcutaneous denosumab 60 mg every 6 months or oral alendronate 70 mg once weekly, then crossed over to the other treatment. The primary endpoint, treatment adherence at 12 months, was 76.6% for alendronate and 87.3% for denosumab.
Introduction The purpose of this study is to evaluate treatment adherence with subcutaneous denosumab 60 mg every 6 months or oral alendronate 70 mg once weekly.
Methods In this multicenter, randomized, open-label, 2-year, crossover study, 250 postmenopausal women with low bone mineral density received denosumab or alendronate for 12 months, then the other treatment for 12 months. The alendronate bottle had a medication event monitoring system cap to monitor administration dates. Definitions were as follows: compliance, receiving both denosumab doses 6 (±1) months apart or 80–100% of alendronate doses; persistence, receiving both denosumab doses and completing the month 12 visit within the visit window or ≥2 alendronate doses in the final month; adherence, achieving both compliance and persistence. This report includes data from the first 12 months.
Results The primary study endpoint, adherence in the first 12 months, was 76.6% (95/124) for alendronate and 87.3% (110/126) for denosumab. Risk ratios for denosumab compared with alendronate at 12 months were 0.58 (p=0.043) for non-adherence, 0.48 (p=0.014) for non-compliance, and 0.54 (p=0.049) for non-persistence. Subject ratings for treatment necessity, preference, and satisfaction were significantly greater for denosumab and ratings for treatment bother were significantly greater for alendronate. Adverse events were reported by 64.1% of alendronate-treated subjects and 72.0% of denosumab-treated subjects (p=0.403). The most common adverse events were arthralgia, back pain, pain in extremity, cough, and headache (each in <10% of subjects in each group).
Conclusions Significantly greater treatment adherence was observed for subcutaneous administration of denosumab every 6 months than for oral alendronate once weekly.

Keywords Adherence · Alendronate · Compliance · Denosumab · Persistence

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Introduction

The lifetime risk of osteoporotic fracture is 40–50% in women and 13–22% in men [1]. Hip fracture is associated with 1.75 million disability-adjusted life-years lost annually [2]. Fractures worsen quality of life in patients with osteoporosis [3] and are associated with significant costs, particularly amongst older patients [4]. Oral bisphosphonates are effective in reducing the risk of osteoporotic fractures [5–7]. However, persistence (continuing treatment for the full duration prescribed), compliance (taking treatment as prescribed), and adherence (the combination of persistence and compliance) to long-term bisphosphonate therapy are often inadequate, leading to suboptimal health outcomes and increased costs [8–11].

Continuous long-term bisphosphonate treatment for 7 years was shown to provide greater skeletal benefits than shorter treatment [12]. However, up to one half of patients are not adherent to their bisphosphonate therapy as prescribed [13], and the majority of patients discontinue bisphosphonate therapy within 1 year [9, 13, 14]. A recent meta-analysis of 236,540 patients in five studies who were followed for 1 year determined that mean persistence with bisphosphonate therapy for osteoporosis was only 184 days [14]. In the same report, meta-analysis of 171,063 patients in six studies that ranged from 1 to 2.5 years in duration found that approximately one third of subjects were non-compliant (i.e., only 67% of prescribed doses of bisphosphonates were actually dispensed) [14]. Non-compliant patients had fracture risks that were 16% higher for non-vertebral fractures, 28% higher for hip fractures, and 43% higher for clinical vertebral fractures as compared with compliant patients [14]. Another analysis of bisphosphonate use among 35,537 women from two claims databases who were followed for up to 2 years determined that women receiving bisphosphonate treatment who had a refill rate of up to 50% gained only marginal benefit from treatment; the benefits increased progressively with increased refill rates beyond 50% [9]. Other analyses have reported that fewer than half of postmenopausal patients are at least 80% adherent to bisphosphonate treatment [15]. These data underscore the need for new osteoporosis treatment options that may improve adherence among postmenopausal women.

Denosumab (Prolia™) is a fully human monoclonal antibody that has high affinity and specificity for RANK ligand (RANKL) [16]. RANKL is the primary mediator of osteoclast activity in many conditions and modulation of the RANKL/RANK interaction has been implicated as a major contributor to the pathogenesis of excess bone resorption and osteoporosis [17]. By inhibiting RANK/RANKL interactions, denosumab reduces osteoclast activity and increases bone mineral density (BMD) and decreases bone turnover markers. The effects are maintained for at least 6 months after a single subcutaneous injection [18]. Use of 6-monthly denosumab injections might improve adherence for a number of reasons: the clinician is responsible for administration of the drug, which allows for control over treatment adherence; patients may prefer 6-monthly injection administration; and dosing irregularities affecting the absorption of oral bisphosphonates (but not denosumab injections) are avoided. Controlled clinical trials have shown that the efficacy of subcutaneous denosumab injections every 6 months to increase bone mineral density and suppress markers of bone resorption is better than that with once-weekly oral alendronate treatment in postmenopausal women [19, 20].

The primary objective of this study was to evaluate adherence (including both compliance and persistence) to 12 months of treatment with subcutaneous denosumab 60 mg every 6 months or oral alendronate 70 mg once weekly in a prospective, open-label, randomized trial.

Methods

Study design

This multicenter, randomized, open-label, 2-year, crossover study enrolled postmenopausal women with low BMD who had not received prior bisphosphonate or denosumab therapy. Subjects entered a screening period of up to 35 days before randomization. Eligible subjects were randomized in a 1:1 allocation to one of two treatment sequences. The computer-generated randomization scheme was prepared by the sponsor before the study using randomly permuted blocks, stratified by center and by prior osteoporotic fracture, and implemented by interactive voice-response system. Subjects in sequence A received denosumab 60 mg subcutaneously every 6 months for 1 year (treatment period 1) followed by alendronate 70 mg orally once weekly for 1 year (treatment period 2). Subjects in sequence B received the same treatments in reverse order (alendronate then denosumab). All subjects received daily calcium (1,000 mg) and vitamin D (≥400 IU) supplementation. Follow-up visits were scheduled for 6, 12, 18, and 24 months. This report includes data from the first 12 months (treatment period 1), including the results of the primary study endpoint, treatment adherence in the first 12 months.

Eligibility criteria

Study participants were required to be ambulatory, postmenopausal, and at least 55 years of age at the start of screening. During the screening period, either a GE Lunar

or a Hologic bone densitometer was used for dual energy X-ray absorptiometry (DXA) assessment. Subjects were required to have BMD T-scores between −4.0 and −2.0 at the lumbar spine, total hip, or femoral neck during screening. At least two lumbar vertebrae or at least one hip were required to be evaluable by DXA.

Subjects were excluded if they had received any prior bisphosphonate or denosumab treatment. Other clinical exclusion criteria were unstable hyper/hypothyroidism, hyper/hypoparathyroidism, hyper/hypocalcemia, impaired hepatic or renal function, history of gastric or duodenal ulcer with significant gastrointestinal bleed requiring hospitalization or transfusion, rheumatoid arthritis, Paget's disease, Cushing's disease, hyperprolactinemia, cirrhosis of the liver, HIV, hepatitis B, hepatitis C, malignancy in the past 5 years, metabolic bone disease, malabsorption, symptomatic vertebral fracture in the past 3 months, solid organ or bone marrow transplant, or vitamin D deficiency (25[OH] vitamin D level <20 ng/mL [<49.9 nmol/L]). Subjects with contraindications to or known sensitivity/intolerance to any study treatment were excluded. Subjects were also excluded if they had received strontium ranelate at any time, PTH or PTH derivatives in the past year, or any of the following in the past 3 months: any SERM (e.g., raloxifene), tibolone, anabolic steroids, testosterone, glucocorticosteroids, systemic hormone replacement therapy, calcitonin, calcitriol, or vitamin D derivatives (except low doses such as those contained in multivitamins), other bone-active drugs including anti-convulsants (except benzodiazepines) and heparin, or chronic systemic ketoconazole, androgens, ACTH, cinacalcet, aluminum, lithium, protease inhibitors, methotrexate, or gonadotropin-releasing hormone agonists.

Written informed consent was obtained for each study participant and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki. An institutional review board or independent ethics committee approved the study protocol for each site.

Treatment

Subjects in the denosumab group received subcutaneous injections of denosumab 60 mg every 6 months, with the doses given at the day 1 and month 6 study visits. Subjects in the alendronate group self-administered alendronate 70 mg orally, with the first dose within 6 days after study day 1, and subsequent doses once weekly (on the same day each week) for 12 months. At each study visit, alendronate was dispensed in a bottle with a special medication event monitoring system (MEMS) cap that recorded opening and closing of the cap to monitor administration dates. Subjects were instructed to open the bottle only to take alendronate and to remove only one tablet each time they opened the bottle.

Outcomes

Adherence to alendronate administration was based on MEMS data to improve precision and accuracy compared with other methods of monitoring dosing. Analyses of adherence counted a maximum of four events (i.e., consumption of four alendronate tablets) per 28-day period when more than four events were recorded by MEMS. Supplementary information on alendronate administration was collected through self-report and pill counts at each follow-up study visit in the alendronate group.

Concomitant medications and adverse events (including clinical fractures) since the prior visit were recorded. At each visit, subjects completed an adaptation of the Beliefs about Medicines Questionnaire (BMQ) [21] that included 22 specific questions in the following three major domains: *necessity* of the prescribed medication for controlling osteoporosis now and in the future, *concerns* about the potential adverse effects of taking the prescribed medication for controlling osteoporosis, and *preference* for one medication over the other. At 6 and 12 months, subjects completed the Bother subscale (five-point scale ranging from "not at all bothered" to "severely bothered") and the Satisfaction subscale (five-point scale from "not at all satisfied" to "very satisfied"), which were taken from the Patient Satisfaction Questionnaire (PSQ) [22]. Subjects completed the BMQ and PSQ questions prior to any other study procedures.

Follow-up measurements of BMD of the lumbar spine and hip were performed at 12 months. The DXA readings were read at the local study sites. Blood samples for hematology, serum chemistry, biomarkers, and anti-denosumab antibody analysis were analyzed at baseline and at 12 months.

Statistical methods

The primary analysis set included all randomized subjects. Subjects with no post-baseline visit were considered as non-adherent, non-compliant and non-persistent. The safety analysis set included all subjects who received at least one dose of study medication. To be included in the safety analysis set, subjects in the alendronate group needed to return for at least one follow-up visit (at 6 or 12 months) to confirm from MEMS data or CRF data that at least one alendronate tablet had been taken. All subjects who received the first injection of denosumab were included in the safety analysis set.

The primary study endpoint was the proportion of subjects in each treatment group who were adherent to treatment at the end of treatment period 1 (12 months). Subjects were considered adherent to treatment if they satisfied the criteria for both compliance and persistence. In the denosumab group, compliance was defined as receiving both injections 6 (±1) months apart and persistence was

defined as receiving both injections and returning for the month 12 visit within the visit window. In the alendronate group, compliance was defined as taking at least 80% of tablets and persistence was defined as taking at least two tablets in the last month and returning for the month 12 visit within the visit window.

The proportion of subjects who were compliant to treatment and the proportion persisting with treatment at the end of treatment period 1 were secondary study endpoints. Point estimates and 95% confidence intervals (CI) were determined for the absolute rate reduction and for the rate ratio between treatment groups for adherence, compliance, and persistence. Other secondary endpoints included time to treatment non-adherence, BMQ scores during treatment period 1, and subject satisfaction scores during treatment period 1. BMD at 12 months was an exploratory endpoint and the study was not powered to detect a difference in BMD between the two treatment groups. For calculation of the percentage change in bone turnover markers, values below the limit of quantitation were set to the limit of quantitation. Safety endpoints included subject incidences of adverse events and subject incidences of serious adverse events (i.e., events that were fatal, life-threatening, or disabling, or that resulted in hospitalization, birth defect, or other significant medical hazard).

Statistical hypothesis tests were conducted at the 0.05 significance level. The primary endpoints were compared between treatment groups using a Cochran Mantel Haenszel test stratified by center and prior osteoporotic fracture. Categorical patient-reported endpoints were compared between treatment groups using a van Elteren non-parametric test, stratified by center and prior osteoporotic fracture. Continuous endpoints were analyzed using analysis of variance stratified by center and prior osteoporotic fracture.

Time to treatment non-adherence was described with Kaplan–Meier methods. Statistical comparisons of this endpoint were not done.

The sample size was based on the primary endpoint and an assumed dropout rate of up to 20% of randomized subjects (10% per treatment period). To detect at least a 20% difference in the proportion of subjects who were adherent to treatment with denosumab compared with alendronate at the end of treatment period 1, a total of 250 subjects (125 subjects in each group) would provide at least 85% power with a two-tailed, 0.05 significance level.

Results

Subject disposition

A total of 250 subjects were enrolled and randomized at 20 centers in the USA and five centers in Canada (Appendix), starting in October 2007, and the final 12-month assessment was completed in June 2009. A total of 124 subjects were assigned to alendronate and 126 subjects were assigned to denosumab in treatment period 1 (Fig. 1). At 12 months, 106 (85.5%) subjects in the alendronate group and 113 (89.7%) subjects in the denosumab group had completed treatment period 1. One (0.8%) subject in the alendronate group and three (2.4%) subjects in the denosumab group crossed over to the opposite treatment early. Other reasons for early termination were as follows (alendronate, denosumab): consent withdrawn (four (3.2%), seven (5.6%)), adverse event (five (4.0%), 0); lost to follow-up (five (4.0%), three (2.4%)), ineligibility determined (two (1.6%), 0), and administrative decision (one (0.8%), 0).

Baseline characteristics

The key baseline characteristics were balanced across denosumab and alendronate groups (Table 1). Most subjects (96.0% alendronate, 91.3% denosumab) were white. Mean age was 65.3 years in the alendronate group and 65.1 years in the denosumab group, with a mean time since menopause of 17.2 and 18.2 years, respectively. Mean BMD T-scores at baseline were similar between the alendronate and denosumab groups at the lumbar spine (−1.9 and −2.0), total hip (−1.6 in each group) and the femoral neck (−2.0 in each group).

Adherence

A total of 95 (76.6%) subjects were adherent to the alendronate treatment, based on MEMS data, and 110 (87.3%) subjects were adherent to the denosumab treatment

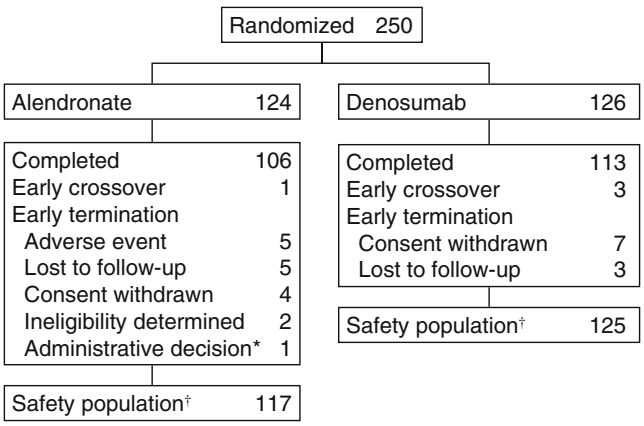

Fig. 1 Subject disposition. *One subject in the alendronate group moved to another city and was unable to return to the study site for subsequent visits; this subject was classified as discontinuing early due to "Administrative Decision." †Includes all subjects who received at least one dose of study medication; subjects in the alendronate group were required to return at least one MEMS bottle to confirm they had received at least one dose of alendronate

Table 1 Baseline demographics and disease characteristics

	Alendronate (n=124)	Denosumab (n=126)
Sex, female (n (%))	124 (100.0)	126 (100.0)
Ethnicity/race (n (%))		
White or Caucasian	119 (96.0)	115 (91.3)
Hispanic or Latino	1 (0.8)	6 (4.8)
Black or African American	2 (1.6)	2 (1.6)
Asian	1 (0.8)	3 (2.4)
Japanese	1 (0.8)	0 (0.0)
Age (years, mean (SD))	65.3 (7.7)	65.1 (7.6)
Years since menopause (mean (SD))	17.2 (10.0)	18.2 (11.4)
Lumbar spine BMD T-score (mean (SD))	−1.89 (1.13)	−2.04 (1.16)
Total hip BMD T-score (mean (SD))	−1.60 (0.76)	−1.60 (0.74)
Femoral neck BMD T-score (mean (SD))	−2.03 (0.62)	−2.01 (0.55)

BMD bone mineral density.

by the end of the first 12 months. Thus, the rate of non-adherence was 23.4% in the alendronate group and 12.7% in the denosumab group (Table 2). Adjusting for investigational site and prior osteoporosis fracture status, the non-adherence rate in the denosumab group was 9.7% (95% CI, 0.3% to 19.0%) lower than in the alendronate group. The relative non-adherence ratio between the denosumab and alendronate groups was 0.58 (95% CI, 0.34 to 0.99; p=0.043), representing a 42% lower risk of non-adherence in the denosumab group.

Adherence to alendronate was 78.2% (97 subjects) based on pill-count data and as noted above, adherence was 76.6% (95 subjects) based on MEMS data. The number of tablets taken based on pill-count data and based on MEMS data correlated well (r=0.71; p<0.001). Due to the differences in dosing schedules, time to alendronate non-adherence was reported continuously, whereas time to denosumab non-adherence was reported at 6 and 12 months (Fig. 2).

Compliance and persistence

During the first 12 months, 97 (78.2%) subjects were compliant to the alendronate treatment and 114 (90.5%) subjects were compliant to the denosumab treatment. Thus, the rate of non-compliance was 21.8% in the alendronate group and 9.5% in the denosumab group (Table 2). Adjusting for investigational site and prior osteoporosis fracture status, the non-compliance rate in the denosumab group was 11.0% (95% CI, 2.2% to 19.7%) lower than in the alendronate group. The relative non-compliance risk ratio between the denosumab and alendronate groups was 0.48 (95% CI, 0.26 to 0.87; p=0.014), representing a 52% relative risk reduction of non-compliance in the denosumab group.

During the first 12 months, 99 (79.8%) subjects were persistent to the alendronate treatment and 113 (89.7%) subjects were persistent to the denosumab treatment. Thus, the rate of non-persistence was 20.2% in the alendronate group and 10.3% in the denosumab group (Table 2). Adjusting for investigational site and prior osteoporosis fracture status, the non-persistence rate in the denosumab group was 8.9% (95% CI, 0.1% to 17.8%) lower than in the alendronate group. The relative non-persistence ratio between the denosumab and alendronate groups was 0.54 (95% CI, 0.30 to 1.00; p=0.049), representing a 46% relative risk reduction of non-persistence in the denosumab group.

Table 2 Subject non-adherence, non-compliance, and non-persistence with treatment

	Crude rate (n (%))		Absolute rate reduction (95% CI)	Rate ratio (95% CI)	p Value
	Alendronate (n=124)	Denosumab (n=126)			
Non-adherence[a]	29 (23.4)	16 (12.7)	9.7 (0.3, 19.0)	0.58 (0.34, 0.99)	0.043
Non-compliance[b]	27 (21.8)	12 (9.5)	11.0 (2.2, 19.7)	0.48 (0.26, 0.87)	0.014
Non-persistence[c]	25 (20.2)	13 (10.3)	8.9 (0.1, 17.8)	0.54 (0.30, 1.00)	0.049

[a] Adherence was defined as satisfying the criteria for both compliance and persistence

[b] Compliance was defined as receiving two denosumab injections 6±1 months apart or ≥80% of weekly doses of alendronate

[c] Persistence was defined as receiving two denosumab injections and completing treatment period 1 (12 months), or taking ≥2 alendronate tablets in the last month and completing treatment period 1

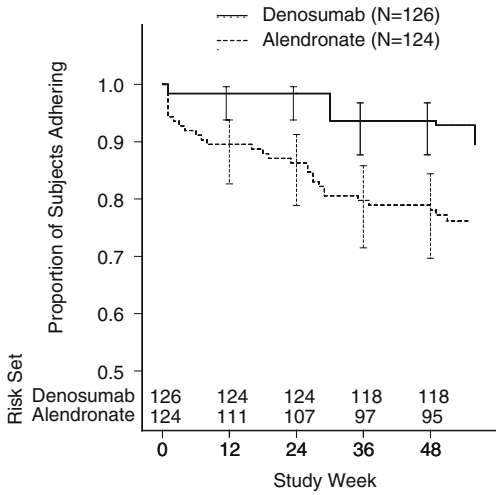

Fig. 2 Time to treatment non-adherence. Subjects in the alendronate group could be non-adherent throughout the first year; subjects in the denosumab group were primarily non-adherent at 6 and 12 months. No statistical comparisons were done for this analysis

Patient-reported outcomes

Scores on the BMQ range from 1 to 5 with a higher score indicating stronger beliefs in necessity or stronger concern or preference. BMQ scores at baseline and 6 months are summarized in Table 3. Mean scores for subject beliefs about the necessity for the prescribed treatment were not significantly different between the alendronate group and the denosumab group at baseline (3.32 vs 3.26, $p=0.491$); however, by 6 months they were significantly lower for alendronate than for denosumab (3.14 vs 3.31, $p=0.024$). Mean scores for subject concerns about potential adverse consequences of treatment were not significantly different between the alendronate group and the denosumab group, either at baseline (2.33 vs 2.43, $p=0.066$) or at 6 months (2.22 vs 2.12, $p=0.135$). However, subject concerns tended to decrease more after exposure to treatment in the denosumab group than in the alendronate group. Subjects reported significantly lower mean preference scores for alendronate than for denosumab both at baseline (2.97 vs 3.47, $p<0.001$) and at 6 months (3.01 vs 3.73, $p<0.001$).

The mean (±SD) score for subject-reported satisfaction at 12 months on a PSQ scale from 1 to 5 (higher scores represented greater satisfaction) was 4.29 (±0.89) for alendronate and 4.59 (±0.87) for denosumab ($p=0.001$). The mean (±SD) score for subject-reported bother at 12 months on a PSQ scale from 1 to 5 (higher scores represented greater bother) was 1.32 (±0.52) for alendronate and 1.11 (±0.21) for denosumab ($p=0.006$).

At 12 months, subjects in the denosumab group were more likely than subjects in the alendronate group to report being either very satisfied or quite satisfied with the dosing frequency, route of administration, convenience, and overall satisfaction with treatment (Fig. 3).

Bone mineral density and bone turnover markers at 12 months

Lumbar spine BMD increased by a mean (±SD) of 4.9% (±3.8%) in the alendronate group and 5.6% (±3.8%) in the denosumab group. Total hip BMD increased by a mean (±SD) of 2.5% (±3.6%) and 3.1% (±3.1%), respectively. Femoral neck BMD increased by a mean (±SD) of 2.0% (±3.6%) and 2.9% (±3.5%), respectively. Serum C-telopeptide decreased by a median (interquartile range) of −68.6% (−80.8%, −50.8%) and −68.7% (−81.3%, −51.9%), respectively. Urinary N-telopeptide decreased by a median (interquartile range) of −66.0% (−74.5%, −54.0%) and −66.9% (−77.0%, −57.1%), respectively.

Safety

The safety population included 117 subjects in the alendronate group and 125 subjects in the denosumab group who received

Table 3 Mean (SD) scores on the Beliefs about Medicines Questionnaire (BMQ)

BMQ Scale[a]	Study visit	Mean (SD)		*p* Value
		Alendronate ($n=115$)	Denosumab ($n=121$)	
Necessity	Baseline	3.32 (0.52)	3.26 (0.48)	0.491
	Month 6	3.14 (0.53)	3.31 (0.61)	0.024
Concern	Baseline	2.33 (0.48)	2.43 (0.46)	0.066
	Month 6	2.22 (0.51)	2.12 (0.52)	0.135
Preference	Baseline	2.97 (0.40)	3.47 (0.43)	<0.001
	Month 6	3.01 (0.53)	3.73 (0.47)	<0.001

[a] Scores on the BMQ range from 1 to 5. Higher scores indicate stronger beliefs about the necessity of the prescribed medication for controlling osteoporosis, greater concerns about the adverse consequences of taking the prescribed medication for controlling osteoporosis, and stronger preference for one medication over the other

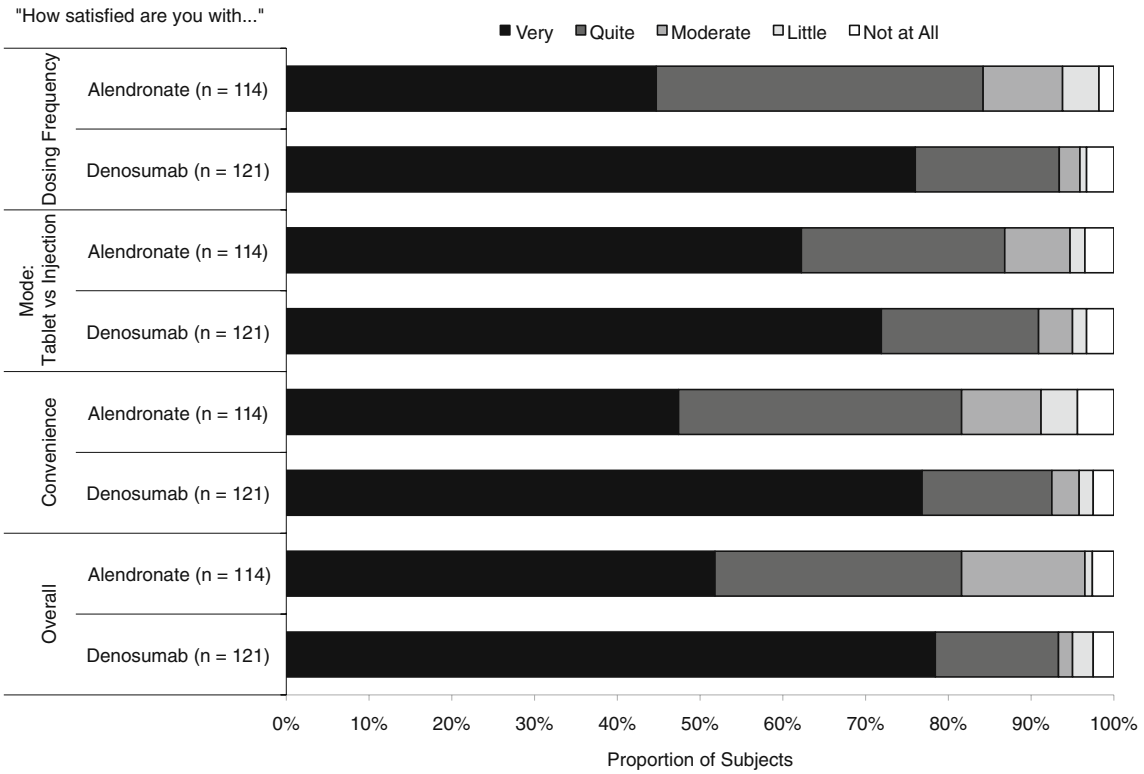

Fig. 3 Subject-reported treatment satisfaction at 12 months

at least one dose of study treatment; subjects in the alendronate group who did not return any MEMS bottles (to confirm they had received at least one dose) were excluded from this population. Of the subjects in the safety population, 75 (64.1%) in the alendronate group and 90 (72.0%) in the denosumab group reported at least one adverse event (p= 0.403). The most commonly reported adverse events were (alendronate, denosumab): arthralgia (eight (6.8%), 11 (8.8%)), back pain (ten (8.5%), five (4.0%)), pain in extremity (four (3.4%), 9 (7.2%)), cough (six (5.1%), five (4.0%)), and headache (seven (6.0%), four (3.2%)). There were no statistically significant differences between groups in the subject incidence of adverse events. Infectious adverse events were reported by 24 (20.5%) subjects in the alendronate group and 33 (26.4%) subjects in the denosumab group (p=0.293). There were no reports of hypocalcemia, skin infection, cancer, or osteonecrosis of the jaw.

A total of five (4.3%) subjects in the alendronate group and three (2.4%) subjects in the denosumab group each reported at least one serious adverse event. Serious adverse events reported by one subject each in the alendronate group were lumbar spinal stenosis, muscle spasms, pain, clostridium difficile colitis, atrial fibrillation, congestive heart failure, and squamous cell carcinoma. Serious adverse events reported by one subject each in the denosumab group were osteoarthritis, chest pain, and diverticulitis.

Discussion

After 12 months in this open-label, randomized clinical trial, significantly more subjects adhered to, complied with, and persisted on denosumab treatment than on alendronate treatment. The relative non-adherence ratio between groups was 0.58, representing a 42% lower risk of non-adherence in the denosumab group than in the alendronate group. This non-adherence difference consisted of both a 52% lower risk of non-compliance and a 46% lower risk of non-persistence. As expected from their dosing schedules, alendronate non-adherence was reported throughout the first year because subjects in this group could start being non-adherent on a weekly basis, whereas denosumab non-adherence occurred at 6 and 12 months when subjects were scheduled for denosumab administration or follow-up visits. Consequently, more subjects completed 12 months of treatment in the denosumab group than in the alendronate group.

By design, the goal of 6-monthly subcutaneous injections is to remove some of the challenges associated with oral therapies. Because denosumab is delivered by injection rather than oral administration, denosumab bioavailability should be optimal. Moreover, the major obstacle to adherence with an injectable therapy is one of persistence; namely, whether the patient returns for follow-up injections. In the case of denosumab, treatment persistence requires only one visit every

6 months. In contrast, persistence to oral bisphosphonate therapy—even when dosed once monthly—requires the patient to self-administer all treatment at the correct dose on the correct schedule and to follow the dosing instructions correctly.

In clinical practice, the actual difference in risk of non-adherence may be even greater than suggested by the values observed in this study. Although the study definition for persistence in both groups included completion of the 12-month visit, subjects in the denosumab group had to receive all (i.e., both) scheduled injections whereas subjects in the alendronate group had to take at least 50% (i.e., two of four) of the weekly alendronate doses in the final month to be considered persistent. Similarly, the definition for compliance was receipt of both doses 6 (±1) months apart in the denosumab group and at least 80% of doses in the alendronate group. Thus, subjects in the denosumab group were required to be 100% persistent and 100% compliant with prescribed treatment, whereas the requirements were somewhat less stringent in the alendronate group. Furthermore, no evaluation of compliance with dosing instructions for subjects in the alendronate group was included in the analysis. Requiring 100% persistence and 100% compliance (i.e., 4 tablets in the last 4 weeks) to be considered adherent to alendronate therapy would have reduced the rate of adherence substantially in this group to only 18.5% instead of 76.6%.

Patient satisfaction and preference for a particular therapy may be important determinants for adherence to therapy in the management of postmenopausal osteoporosis [23, 24]. In this study, subjects reported greater bother with weekly oral alendronate. Conversely, subjects reported greater satisfaction with 6-monthly denosumab injections overall, as well as for dosing frequency, route of administration, and convenience. Subject-reported scores on the BMQ demonstrated no difference at baseline for beliefs about the necessity for each treatment, but after 6 months of treatment, subjects reported significantly higher scores for the necessity of denosumab than for alendronate. Subjects also reported significantly higher preference scores for denosumab than for alendronate, both at baseline and at 6 months. Subjects expressed similar levels of concern about potential adverse events with both treatments at baseline and at 6 months.

Adverse events and serious adverse events generally occurred with similar frequency between the groups during the first 12 months, consistent with findings of previous head-to-head controlled trials of denosumab and alendronate [19, 20, 25, 26]. Although not the primary focus of the study, BMD and bone turnover marker outcomes were also consistent with the findings of previous randomized, controlled trials of denosumab and alendronate [19, 20, 25, 26]. Increases in BMD were seen at the lumbar spine, total hip, and femoral neck in both treatment groups and decreases in the turnover markers, serum C-telopeptide and urinary N-telopeptide, were also seen in both treatment groups.

Most previous studies of bisphosphonate treatment preference and adherence have either used non-interventional designs [13, 24, 27], or they have been randomized studies that included questions about treatment preference but not about adherence [28–32]. Few studies have prospectively evaluated bisphosphonate treatment adherence [33, 34]. Because this study used a prospective, randomized design, it allowed for statistical comparisons between treatment groups and reduced potential confounding associated with retrospective analyses, such as comorbid conditions and treatment selection based on patient characteristics.

Additionally, most previous studies have focused on the influence of dosing frequency (daily, weekly, or monthly) for oral bisphosphonate therapy on patient preference [13, 24, 27–31]. In one randomized, double-blind, head-to-head study, patients preferred once-annual intravenous zoledronic acid therapy to once-weekly oral alendronate therapy [32]. Two other randomized, double-blind, head-to-head studies that used a validated questionnaire [22] at the end of treatment reported that patients preferred, were more satisfied, and were less bothered by 6-monthly subcutaneous injections of denosumab than weekly oral alendronate therapy [35]. However, each of the latter three studies used double-blind, double-dummy, parallel-group designs in which subjects received both the injectable treatment (denosumab/zoledronic acid or placebo) and oral treatment (alendronate or placebo). The present study used an open-label, crossover design in which all subjects were scheduled to receive each treatment for 12 months and used validated questionnaires at several visits to assess medication beliefs [21] and preferences [22]. Use of assessments at baseline and 6 months provided additional insights into subject adherence behavior. An established body of research, across a number of disease categories has shown that a subject's beliefs are related to medication adherence [36–39]. Specifically, it has been shown that adherence to therapy is partially related to a subject's beliefs regarding the necessity of the medication relative to their beliefs regarding concerns with the potential for adverse events [40]. This study lends support to this basic idea because subjects were more adherent to denosumab treatment than to alendronate treatment and at 6 months they reported significantly greater necessity scores for denosumab than for alendronate and numerically greater concerns scores for alendronate than for denosumab. Additional insights into the differences between groups with respect to adherence were provided by the finding that at both baseline and 6 months subjects in the denosumab group reported greater preference scores than subjects in the alendronate group. Because the primary study endpoint was assessed after 12 months, this analysis included patient-reported outcomes before subjects crossed over to the alternate treatment group for an additional 12 months. Patient-reported outcomes at

months 18 and 24 are not yet available but should provide additional insight into patient beliefs and preferences after subjects have had experience with both treatments.

This study design may have several limitations. Because the study was designed to approximate treatment compliance in actual clinical practice, subjects could not be blinded to treatment assignment which may introduce bias [41]. Subjects who agreed to participate in the study were willing to receive both oral and injectable therapy and participate in a 2-year study, resulting in a likely self-selection bias for subjects who were more likely to adhere to treatment. Subjects also knew the purpose of the study, which might have resulted in increased adherence in both treatment groups compared with actual clinical practice. Additionally, subjects knew that their adherence to oral alendronate treatment was monitored by MEMS, which might have increased treatment adherence in the alendronate group. Collectively, these limitations could have increased the adherence rate in both treatment groups. This is supported by the finding that fewer than 25% of subjects in the alendronate group of this study were non-adherent (23.4%), non-compliant (21.8%), and non-persistent (20.2%) during the first 12 months, whereas previous analyses have reported that approximately one third to one half of patients in clinical practice do not take bisphosphonate therapy as prescribed [13, 14].

This study used MEMS data to record the dates subjects in the alendronate group opened their study medication bottles. Subjects were instructed to open the bottle only when they took medication and to remove only one pill each time they opened the bottle. Study medication accounting was done by pill count at the site visits, and a significant correlation was seen between the MEMS (76.6%) and pill-count estimates (78.2%) of treatment adherence, which suggests that most subjects used the MEMS bottles as directed. The MEMS method was used in previous bisphosphonate studies to measure study medication administration [33, 34]. In one of those studies, adherence to once-daily oral risedronate treatment at 1 year was approximately 80% [33], which was much higher than reported in other studies of adherence to oral bisphosphonate therapy [9, 13, 14]. Thus, as noted above, when subjects know their adherence is being monitored by MEMS they may be more likely to adhere to treatment, which might have increased adherence rates during alendronate treatment in this study. In addition, visits with a healthcare professional are known to favorably influence adherence to medication. In any clinical trial, regular visits with a skilled healthcare professional are required by protocol and this may differ significantly from routine practice.

In conclusion, the primary outcome of treatment adherence during the first 12 months of this prospective, randomized, crossover study was significantly greater for subjects who received subcutaneous administration of denosumab 60 mg every 6 months compared with subjects who took oral alendronate 70 mg once weekly. Subjects in the denosumab group were more likely to report being satisfied with the dosing schedule and route of administration for denosumab, as well as its convenience, and they reported less bother and greater preference for denosumab compared with alendronate.

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M Lillestol is an investigator for Amgen and reports financial disclosures for Alexion, Amgen, Astra/Zeneca, Bausch & Lomb, BioSante, Boehringer Ingelheim, Bristol Myers Squibb, CombinatoRx, Covance, Daiichi Sankyo, DP Clinical, Endo Pharmaceuticals, Forest, GlaxoSmithKline, Hisamitsu, i3 Research, Lilly, Novartis, Novo Nordisk, NPS Allelix, NPS Pharmaceuticals, Otsuka, Pfizer, PPD, Quintiles, Roche, Sanofi-Aventis, Schering-Plough, Sepacor,Smith Kline Beecham, Takeda, Viropharma, and Wyeth.

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J Borenstein previously was employed by Amgen.

S Satram-Hoang has served as a consultant for Amgen.

YC Yang, P Kaur, D Macarios and S Siddhanti are employees and shareholders of Amgen.

Appendix

The DAPS (Denosumab Adherence Preference Satisfaction) study investigators were as follows, listed alphabetically by country: USA—Bruce Akright, Kurt Datz, Ara Dikranian, Elyse Erlich, Stephen Fehnel, Catherine Gerrish, John Joseph, Robert Lang, Leroy Leeds, Michael Lillestol, Dennis Linden, Michael McClung, Jefferey Michelson, Alfred Moffett, Constantine Saadeh, Gerald Shockey, Joseph Soufer, Raul Tamayo, and John Williams; Canada—Jonathan Adachi, Stephanie Kaiser, David Kendler, Jean-Pierre Raynauld, and Jerieta Waltin-James.

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