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ORIGINAL ARTICLE

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Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: a double-blind, randomized study

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Abstract The efficacy and safety of treatment with oral alendronate (ALN) 35 mg once weekly for 52 weeks were compared with those of ALN 5 mg once daily in a double-blind, randomized, multicenter study of Japanese patients with involutional osteoporosis. The primary efficacy end point was the percent change from baseline in the lumbar spine (L1–L4) bone mineral density (BMD) after 52 weeks of treatment. In this study, 328 patients were randomized to ALN 5 mg once daily (160 patients) or ALN 35 mg once weekly (168 patients). The adjusted mean percent change from baseline in lumbar spine (L1–L4) BMD after 52 weeks of treatment was 5.8% and 6.4% in the once-daily group and the once-weekly group, respectively (both $P < 0.001$). The 95% confidence interval for the difference in spine BMD change between the two treatment groups was –0.31% to 1.48%, indicating that the two regimens were therapeutically equivalent, since the confidence interval fell entirely within the predefined equivalence criterion (±1.5%). The time course of the spine BMD increase was also similar for both regimens. Regarding total hip BMD, mean changes from baseline at 52 weeks were 2.8% and 3.0% in the once-daily group and the once-weekly group, respectively. In addition, the bone markers (urinary deoxypyridinoline, urinary type-I collagen N-telopeptides, and serum bone-specific alkaline phosphatase) were reduced to a similar level by either treatment throughout the treatment period. The tolerability and safety profiles were also similar between the treatment groups. Taken together, we conclude that the efficacy and safety of the ALN 35-mg once-weekly regimen are therapeutically equivalent to those of the ALN 5-mg once-daily regimen.

Key words Alendronate · Involutional osteoporosis · Bone markers · BMD

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Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to increased risk of fracture; bone strength reflects the integrated contributions of properties that include bone density, turnover, and microarchitecture [1,2]. The number of patients afflicted with osteoporosis is very large and increases each year in developed nations with aging populations. For example, there were approximately 11 million patients with osteoporosis in Japan in 2002 [3]. The incidence of osteoporosis-associated vertebral fracture increases with age; the estimated incidence in Japanese women is 40 per 1000 person-years for ages 70–79 and 84 per 1000 person-years for ages 80–89 [4].

Alendronate (ALN) is a nitrogen-containing bisphosphonate that is used in many countries to treat osteoporosis, and it has been extensively evaluated in clinical trials of up to 10 years duration. These trials have demonstrated that ALN has consistent efficacy in restoring bone turnover to normal levels, increasing bone mass, and reducing fracture risk [5–23]. Although daily treatment is gener-

ally well tolerated, most patients would prefer a weekly regimen, partly because oral bisphosphonates must be taken in a fasting state at least 30 min before consuming food or beverages (other than water). In the previous study (~96% Caucasian), the therapeutic equivalence of 70 mg ALN once weekly and 10 mg ALN daily was demonstrated in postmenopausal patients with osteoporosis, based on percent change in lumbar spine bone mineral density (BMD). The safety profile was comparable in the weekly and daily treatment groups in these studies [24,25].

Previous studies demonstrated that 5 mg ALN daily produced effects on bone in Japanese that were similar to those obtained using the 10-mg dose in Caucasians [19]. Consequently, the standard dose of ALN in Japan is 5 mg daily. However, the effects of 35 mg ALN once weekly have not been compared with those of 5 mg daily in Japanese. The present study was carried out in a double-blind manner in a Japanese patient population with involutional osteoporosis to compare the efficacy and safety of oral ALN 35 mg once weekly to 5 mg once daily over a 52-week period.

Patients and methods

Study design

This study was a 52-week, randomized, double-blind, multicenter, comparative trial in Japanese patients with involutional osteoporosis to compare the efficacy and safety of ALN 35 mg once weekly with those of ALN 5 mg once daily. All study staff and patients were blinded to allocation and treatment. All study medications were provided by Merck, Whitehouse Station, NJ, USA, and Banyu Pharmaceutical, Tokyo, Japan. Patients were randomized to receive either one tablet of ALN 35 mg once a week and one tablet of ALN 5 mg placebo every day (ALN 35-mg once-weekly group) or one tablet of ALN 5 mg daily and one tablet of ALN 35 mg placebo once a week (ALN 5-mg once-daily group). The study drug was allocated in a 1:1 ratio according to a randomized allocation table made by an independent organization. The patients received the study drug in the order of their enrollment at each site. All study drugs were taken orally with approximately 180 ml of water upon waking in the morning. Patients were instructed to keep their upper body upright and refrain from any food, beverage, or other drug intake for at least 30 min after dosing. One tablet of Calcichew D3 (containing 500 mg elemental calcium and 200 IU vitamin D3, Fujisawa Pharmaceutical, Osaka, Japan) was taken after the evening meal throughout the treatment period.

The study was conducted from March 2002 through October 2003, and was approved by the individual institutional review boards of the 35 participating sites (36 departments). Written informed consent was obtained from all patients enrolled, in accordance with the spirit of the Declaration of Helsinki and the Guideline for Good Clinical Practice (Ordinance of Ministry of Health, Labour and Welfare of Japan, March 27, 1997).

Subject population

At the start of the observation period, subjects were required to be ambulatory men or women aged 43 to 90 years; women were at least 2 years postmenopause. The patients were also required to have no evidence of vertebral fractures in at least three vertebrae in the L1 to L4 region on lumbar spine radiographs, and to be less than 70% of young adult mean (YAM) in lumbar spine (L2–L4) BMD, or to be less than 80% of YAM with a history of or current fragility fracture related to osteoporosis. Patients who had been treated in the past 6 months with etidronate at a dose >200 mg/day, or with other bisphosphonates (ALN, etidronate ≤200 mg/day, etc.) for ≥2 weeks were excluded.

Measurement of vertebral BMD and femoral BMD

BMD of lumbar spine (mean of L1–L4) and total hip were measured by dual-energy X-ray absorptiometry (DXA; Hologic, Bedford, MA, USA) at the start of the pretreatment observation period (2–12 weeks, depending on prior medication use), and at the start (baseline) and at weeks 12, 24, and 52 of the treatment period, or at discontinuation. The percent changes in spine and hip BMD from the start of the study drug were calculated at weeks 12, 24, and 52. After measurement, the BMD data and precision control data were forwarded, together with the thoracolumbar radiographs at baseline and lumbar radiographs at weeks 24 and 52, to the Bone Density Evaluation Committee (specifically formed for the present study, led by Prof. M. Fukunaga, Kawasaki Medical School, Okayama) to verify data quality. An auxiliary positioning instrument was used for measuring femoral BMD.

Measurement of bone markers

Biochemical markers of bone turnover, urinary deoxypyridinoline (DPD), urinary type-I collagen N-telopeptides (NTx), and serum bone-specific alkaline phosphatase (BAP), were measured by SRL Medisearch (Tokyo, Japan) at the start of the observation period and at the start and at weeks 4, 12, 24, and 52 of the treatment period, or at discontinuation. Urinary parameters were adjusted by creatinine excretion.

Safety evaluation

Safety of the study drugs was assessed using reported adverse events (AEs) and abnormal laboratory test values. The following laboratory tests were performed: hematology (red blood cell count, white blood cell count, differential white blood cells, hemoglobin, hematocrit, and platelet count), blood chemistry [albumin, total bilirubin, AST (GOT), ALT (GPT), γ-GTP, alkaline phosphatase (AL-P), LDH, CPK, BUN, serum creatinine, total cholesterol, Na, K, Ca and P], and urinalysis (protein and glucose). Fractures in the upper or lower extremities reported by investigators at each site were also included.

Statistical analyses

The primary analysis comparing the efficacy of the two regimens (ALN 35 mg once weekly and 5 mg once daily) used a per protocol set (PPS). In the PPS analysis, patients with important protocol deviations were excluded from the analyses. (A list of protocol violators was issued before unblinding the database). No missing data were imputed. Safety was evaluated in patients who received at least one dose of study drug in the treatment period. The level of statistical significance was two-sided 5% in every analysis.

The primary efficacy end point was percent change from baseline (i.e., the initiation of the treatment period) in lumbar spine (L1–L4) BMD at week 52, calculated as the least-squares (LS) mean difference between treatment groups and its 95% confidence interval (CI) from an analysis of variance (ANOVA) model that included treatment group and center as factors. The two treatments were considered therapeutically equivalent if the 95% CI of the between-group difference in spine BMD change fell entirely within the prespecified bounds of ±1.5%. Similar ANOVA models were used to calculate the least-squares mean difference of percent changes from baseline in lumbar spine BMD at weeks 12 and 24, as well as mean percent changes from baseline in total hip BMD at weeks 12, 24, and 52 and geometric mean percent changes in bone markers at weeks 4, 12, 24, and 52.

Safety and tolerability were assessed by clinical and/or statistical assessment of all relevant safety parameters, including adverse experiences, laboratory values, and vital signs. The incidence of clinical and laboratory AEs and drug-related AEs was calculated for each treatment regimen, and comparisons between the once-daily group and once-weekly group were performed using Fisher's exact test. The discontinuation rate due to drug-related adverse experiences was also calculated and compared between the two treatment groups using Fisher's exact test.

Results

Patient allocation

A total of 328 patients were randomized. After excluding four patients because they did not take the study drug or no efficacy/safety data were available, 324 patients were included in the safety analysis; 156 in the once-daily group and 168 in the once-weekly group. Of the 328 patients randomized, 277 (84.5%) completed the study, while 51 patients (15.5%) were discontinued; 24 in the once-daily group and 27 in the once-weekly group. Major reasons for discontinuation were manifestation of adverse experiences (18 in the once-daily group and 19 in the once-weekly group) or failure to meet the inclusion/exclusion criteria (two in the once-daily group and two in the once-weekly group). For the primary efficacy assessment, the PPS analysis included 297 patients; 150 in the once-daily group and 147 in the once-weekly group. Table 1 shows the baseline characteristics of the 324 patients who were included in the safety analysis, with no significant difference between the two treatment groups.

Lumbar spine and total hip BMD

After 52 weeks of treatment, the LS means of percent change from baseline in spine BMD in the ALN 5-mg once-daily and the 35-mg once-weekly treatment groups were 5.76% and 6.35%, respectively (Table 2). These represent statistically significant increases compared with baseline ($P < 0.001$ for both groups). The LS mean difference (95% CI) of the percent change from baseline in the lumbar spine BMD between the two groups was 0.58% (95% CI; –0.31, 1.48), thereby meeting the prespecified criterion for equivalence, since the 95% CI fell entirely within the bounds of ±1.5% (Table 2). Moreover, the two dose regimens were not significantly different, since the 95% CI of the mean difference between groups included zero. The LS means of the percent change from baseline in the total hip BMD after 52 weeks in the once-daily and once-weekly groups were 2.81% and 2.96%, respectively (Table 2), representing statistically significant increases compared with

Table 1. Baseline characteristics of the patients ($n = 324$)

Characteristics	Dosing regimen of ALN	
	5 mg once daily ($n = 156$)	35 mg once weekly ($n = 168$)
Sex, no. (%)		
Female	149 (96)	163 (97)
Male	7 (4)	5 (3)
Age, years	67.4 (6.9)	66.0 (6.9)
Height, cm	149.6 (6.8)	150.3 (5.5)
Body weight, kg	48.6 (6.3)	49.5 (6.9)
BMI, kg/m^2	21.7 (2.6)	21.9 (2.9)
Spine BMD (L1–L4), g/cm^2	0.62 (0.06)	0.62 (0.06)
Total Hip BMD, g/cm^2	0.65 (0.08)	0.66 (0.09)

All values are presented as mean (SD), except sex
BMI, body mass index; BMD, bone mineral density; ALN, alendronate

Table 2. Percent change from baseline in lumbar spine and total hip BMD at week 52

Site	Dosing regimen of ALN		Intergroup difference
	5 mg once daily	35 mg once weekly	
Spine	5.76 (4.98, 6.55)	6.35 (5.58, 7.11)	0.58 (–0.31, 1.48)
Total hip	2.81 (2.10, 3.51)	2.96 (2.27, 3.65)	0.15 (–0.65, 0.95)

Values are presented as mean (95% confidence intervals). Analyses based on the per protocol set

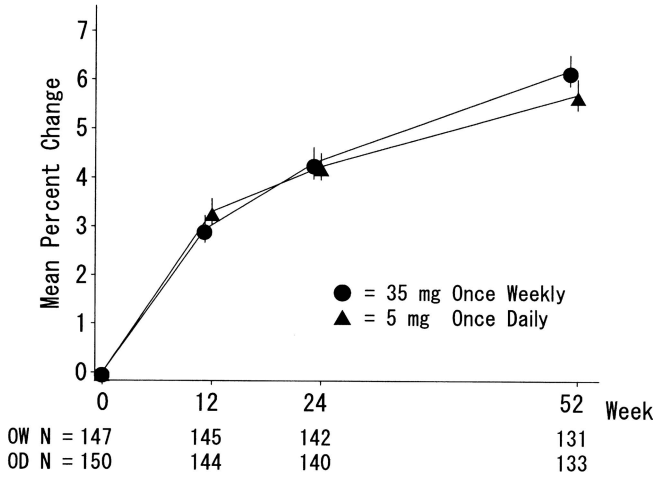

Fig. 1. Mean percent change from baseline in the lumbar spine (L1–L4) bone mineral density (BMD) (mean ± SE). *OW*, once weekly; *OD*, once daily

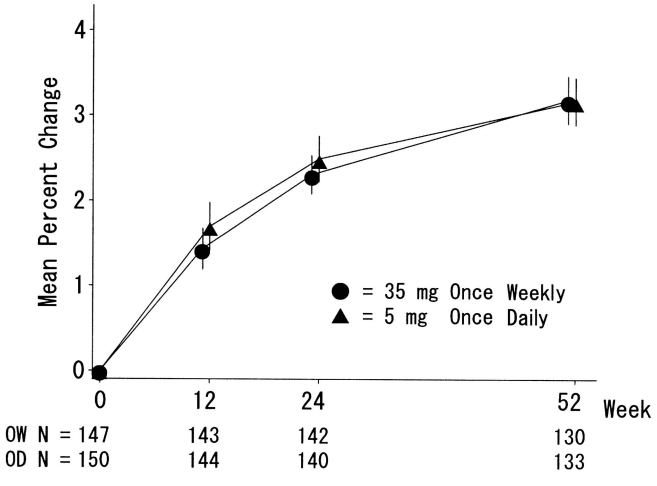

Fig. 2. Mean percent change from baseline in total hip BMD (mean ± SE)

baseline ($P < 0.001$ for both groups). Figures 1 and 2 show the time course of percent BMD change in the lumbar spine and total hip for the two ALN treatment groups. BMD increased significantly ($P < 0.001$) at each time point of measurement in both the spine and total hip, with a similar profile of BMD changes over time for both treatments.

Bone markers (DPD, NTx, and BAP)

The time course of geometric mean percent change from baseline in bone markers (urinary DPD, urinary NTx, and serum BAP) is shown in Fig. 3. In both ALN treatment groups, all three markers were decreased significantly during the period from 4 weeks to 52 weeks ($P < 0.001$ at each measurement point for DPD and NTx; $P \leq 0.017$ for BAP). The geometric mean percent change at week 52 in the once-daily and once-weekly groups, respectively, were –42.0% and –44.9% for DPD (Fig. 3a), –49.2% and –51.5% for NTx (Fig. 3b), and –50.3% and –52.1% for BAP (Fig. 3c). The bone markers (DPD, NTx, and BAP) were thus reduced to a similar level by either treatment throughout the treatment period.

Safety

The incidence of clinical AEs was 89.7% (140/156 patients) in the once-daily group and 85.1% (143/168 patients) in the once-weekly group, with no significant difference between the treatment groups (Table 3). The incidence of drug-related clinical AEs was 17.9% (28/156 patients) in the once-daily group and 13.1% (22/168 patients) in the once-weekly group. Regarding upper gastrointestinal AEs, which have been the major issue with respect to the safety of ALN (and other related drugs), the incidence of drug-related upper gastrointestinal AEs was 9.0% (14/156 patients) and 10.7% (18/168 patients), respectively, in the once-daily and once-weekly groups, with no statistical difference between the treatment groups. The discontinuation rates due to clinical drug-related AEs in the once-daily and once-weekly groups were 8.3% (13/156 patients) and 5.4% (9/168 patients), respectively, with no statistical difference between the treatment groups. Serious AEs were reported in 7 patients in the once-daily group and 11 patients in the once-weekly group. Among those, two patients in the once-daily group had serious AEs that were judged to be drug-related (one case was reflux esophagitis, and the other was aggravation of allergic bowel syndrome). No drug-related laboratory AE occurred at an incidence of more than 3%. None of the laboratory AEs were serious or resulted in discontinuation. The number of patients with new fractures in the upper and lower extremities was two in the once-daily group and three in the once-weekly group.

No remarkable differences were observed between the two groups with regard to any of the safety parameters.

Discussion

This study demonstrated that the effects of daily 5 mg and weekly 35 mg ALN were similar with regard to changes in BMD of the lumbar spine and hip and biochemical markers of bone turnover during 1 year of followup; safety and tolerability were also similar for both dosing regimens. Based upon the prespecified statistical criterion, the 5-mg-daily and 35-mg-weekly dosing regimens were declared therapeutically equivalent. Supporting evidence comes from a recent pharmacokinetic study in Japanese, which reported that the urinary excretion rate of oral ALN 35 mg was similar to that of ALN 5 mg, as was the safety and tolerability profile [26]. The similar urinary excretion rate of ALN 35 mg and 5 mg indicates that overall the same amount of ALN is obtained from each regimen.

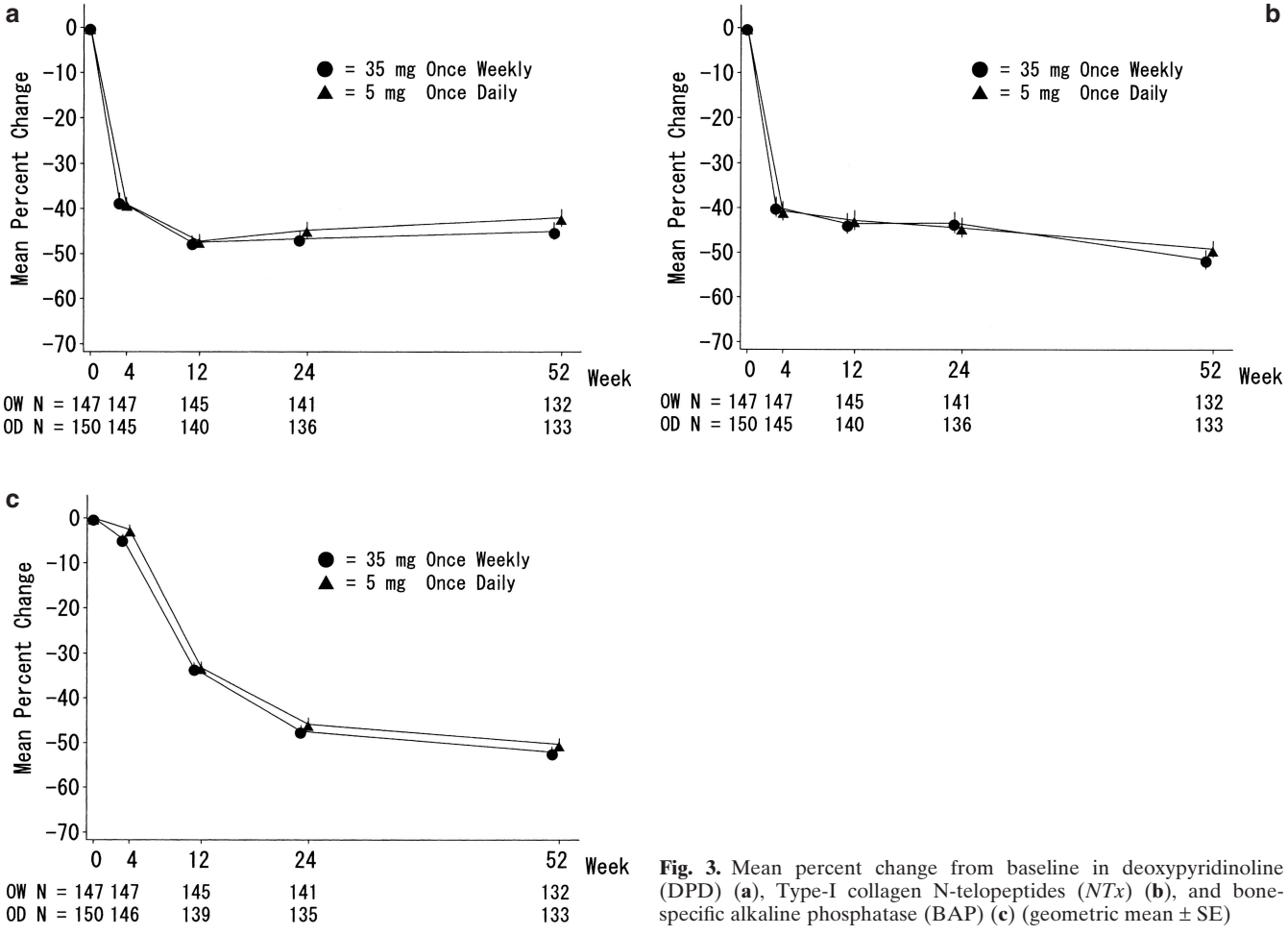

Fig. 3. Mean percent change from baseline in deoxypyridinoline (DPD) (**a**), Type-I collagen N-telopeptides (*NTx*) (**b**), and bone-specific alkaline phosphatase (BAP) (**c**) (geometric mean ± SE)

Table 3. Summary of clinical adverse events (AEs)

	Total *n* (%)	Dosing regimen of ALN	
		5 mg once daily *n* (%)	35 mg once weekly *n* (%)
No. of patients	324	156	168
Any AE	283 (87.3)	140 (89.7)	143 (85.1)
Drug-related AE	50 (15.4)	28 (17.9)	22 (13.1)
Serious AE	18 (5.6)	7 (4.5)	11 (6.5)
Serious drug-related AE	2 (0.6)	2 (1.3)	0 (0.0)
Discontinued due to AE	37 (11.4)	18 (11.5)	19 (11.3)
Discontinued due to drug-related AE	22 (6.8)	13 (8.3)	9 (5.4)
Discontinued due to serious AE	7 (2.2)	4 (2.6)	3 (1.8)
Discontinued due to serious drug-related AE	2 (0.6)	2 (1.3)	0 (0.0)

Less frequent dosing with any medication may improve compliance and thereby improve efficacy [24,27]. The mechanism of action, together with animal studies, predicts that weekly dosing with ALN should provide efficacy that is equivalent to comparable cumulative daily dosing, without compromising safety and tolerability. This result is because bisphosphonates bind to active bone remodeling sites and remain there for extended periods; at sufficient concentrations, this effectively inhibits osteoclastic bone resorption throughout the typical 2–3 week resorption phase of bone remodeling [24,28]. Less frequent (such as weekly) bisphosphonate dosing might also reduce the risk of upper gastrointestinal irritation [24,28]. ALN has demonstrated unsurpassed efficacy with regard to restoring bone turnover

to premenopausal levels, increasing bone density, and reducing the risk of all types of fractures including hip fractures. Furthermore, extensive experience with ALN in clinical trials of up to 10 years' duration has demonstrated continued efficacy and a good safety and tolerability profile [16].

A single criterion for evaluating the therapeutic equivalence of treatment groups based on changes in BMD has not been well established. In a previous study of Caucasians, equivalence was declared when the 90% CI of the difference in spine BMD change between the two groups (daily 10 mg and weekly 70 mg ALN) fell within the range of ±1.5% [24]. In the current study, we used a somewhat stricter criterion, requiring the 95% CI of the difference between the two groups in spine BMD change to fall entirely within a range of ±1.5% to establish equivalence. When the results of this study were compared with the results from the Caucasian study [24], the percent changes from baseline in the lumbar spine (L1–L4) BMD were similar.

Regarding the safety of ALN in the present study, the incidence of AEs overall and gastrointestinal AEs (including upper gastrointestinal AEs and drug-related AEs) did not differ significantly between the treatment groups. These findings are consistent with those observed in Caucasian patients with osteoporosis [24]. Furthermore, a placebo-controlled clinical trial and an endoscopy study both reported that oral administration of ALN 70 mg once weekly had a safety and tolerability profile similar to that of a placebo [29,30]. The lack of differences in upper gastrointestinal AEs between daily 5 mg and weekly 35 mg in our study suggests that the weekly 35 mg dose may not increase the risk of upper gastrointestinal events in Japanese patients with osteoporosis, if administered appropriately [31].

A trial in the United States that surveyed patients who had received treatment with both once-daily and once-weekly ALN in a cross-over design showed that the large majority of patients preferred the 70-mg once-weekly regimen compared with the 10-mg once-daily regimen [32]. Similarly, in a separate, multinational study, which included 406 postmenopausal women with osteoporosis from 19 countries, 84% of patients preferred the once-weekly over the once-daily regimen [33]. In actual medical practice, the once-weekly formulation is now in extensive use, accounting for about 90% of new prescriptions for ALN. Although some patients may wish to take the once-daily formulation for various reasons, the existence of the once-weekly formulation will provide patients with a broader range of treatment options. As noted earlier, oral drug compliance is increased if the frequency of drug administration is reduced [27]. Accordingly, it can be surmised that increasing the convenience of ALN by reducing the frequency of administration to once weekly will increase patient acceptance of treatment of osteoporosis, compliance, and continuation of therapy, leading to better long-term benefits.

In conclusion, our data confirmed that the effects of a weekly 35-mg dose of ALN were similar to those of a daily 5-mg dose in Japanese patients with osteoporosis. The safety and tolerability profiles of both regimens were also similar to each other. These data, together with previous findings, suggest that weekly dosing with ALN provides an alternative that is more convenient and preferred by many patients, which may result in better patient acceptance and continuation of therapy.

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References

1. Consensus Development Conference (1993) Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 94:646–650
2. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy (2001) Osteoporosis prevention, diagnosis, and therapy. JAMA 285:785–795
3. Japan Osteoporosis Society Working Group (2002) Guideline to Clinical Evaluation Methods for Agents Used in Treatment of Osteoporosis, 2002 Revised Edition (in Japanese). Osteoporos Jpn 10:7–79
4. Fujiwara S, Kasagi F, Masunari N, Naito K, Suzuki G, Fukunaga M (2003) Fracture prediction from bone mineral density in Japanese men and women. J Bone Miner Res 18:1547–1553
5. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 348:1535–1541
6. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the fracture intervention trial. JAMA 280:2077–2082
7. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M, Seeman E, Recker RR, Capizzi T, Santora AC II, Lombardi A, Shah RV, Hirsch LJ, Karpf DB (1995) Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 333:1437–1443
8. Tucci JR, Tonino RP, Emkey RD, Peverly CA, Kher U, Santora II AC (1996) Effect of three years of oral alendronate treatment in

postmenopausal women with osteoporosis. Am J Med 101:488–501
9. Devogelaer JP, Broll H, Correa-Rotter R, Cumming DC, Nagant de Deuxchaisnes C, et al. (1996) Oral alendronate induces progressive increases in bone mass of the spine, hip, and total body over 3 years in postmenopausal women with osteoporosis. Bone 18:141–150
10. Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston CC Jr, Adami S, Harris ST, Santora AC II, Hirsch LJ, Oppenheimer L, Thompson D (1997) Prevention of nonvertebral fractures by alendronate. A meta-analysis. JAMA 277:1159–1164
11. Sharpe M, Noble S, Spencer CM (2001) Alendronate: an update of its use in osteoporosis. Drugs 61:999–1039
12. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, Black D, Adachi J, Shea B, Tugwell P, Guyatt G (2002) II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 23:508–516
13. Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, Bone HG, Santora AC, Wu M, Desai R, Ross PD (2000) Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. J Clin Endocrinol Metab 85:3109–3115
14. Pols HA, Felsenberg D, Hanley DA, Stepán J, Muñoz-Torres M, Wilkin TJ, Qin-sheng G, Galich AM, Vandormael K, Yates AJ, Stych B (1999) Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Osteoporos Int 9:461–468
15. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, Nevitt MC, Suryawanshi S, Cummings SR (2000) Fracture risk reduction with alendronate in women with osteoporosis: the fracture intervention trial. J Clin Endocrinol Metab 85:4118–4124
16. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA (2004) Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350:1189–1199
17. Wehren LE, Hosking D, Hochberg MC (2004) Putting evidence-based medicine into clinical practice: comparing anti-resorptive agents for the treatment of osteoporosis. Curr Med Res Opin 20:525–531
18. Shiraki M, Kushida K, Fukunaga M, Kishimoto H, Kaneda K, Minaguchi H, Inoue T, Tomita A, Nagata Y, Nakashima M, Orimo H (1998) A placebo-controlled, single-blind study to determine the appropriate alendronate dosage in postmenopausal Japanese patients with osteoporosis. Endocr J 45:191–201
19. Nakamura T, Kushida K, Shiraki M, Fukunaga M, Taga M, Kishimoto H, Tomita A, Inoue T, Minaguchi H, Kaneda K, Nagata Y, Nakashima M, Orimo H (1998) A double-blind, dose-ranging study of alendronate in patients with involutional osteoporosis, osteoporotic osteopenia or artificial menopause (in Japanese). Med Consult New Remedy 35:3–17
20. Kishimoto H, Shiraki M, Fukunaga M, Kushida K, Kaneda K, Inoue T, Tomita A, Yamamoto K, Orimo H (1998) A long-term study of alendronate in patients with involutional osteoporosis (in Japanese). Med Consult New Remedy 35:19–41
21. Shiraki M, Kushida K, Fukunaga M, Kishimoto H, Taga M, Nakamura T, Kaneda K, Minaguchi H, Inoue T, Morii H, Tomita A, Yamamoto K, Nagata Y, Nakashima M, Orimo H (1999) A double-masked multicenter comparative study between alendronate and alfacalcidol in Japanese patients with osteoporosis. Osteoporos Int 10:183–192
22. Kushida K, Shiraki M, Nakamura T, Kishimoto H, Morii H, Yamamoto K, Kaneda K, Fukunaga M, Inoue T, Nakashima M, Orimo H (2002) The efficacy of alendronate in reducing the risk for vertebral fracture in Japanese patients with osteoporosis: a randomized, double-blind, active-controlled, double-dummy trial. Curr Ther Res 63:606–620
23. Kushida K, Shiraki M, Nakamura T, Kishimoto H, Morii H, Yamamoto K, Kaneda K, Fukunaga M, Inoue T, Nakashima M, Orimo H (2004) Alendronate reduced vertebral fracture risk in postmenopausal Japanese women with osteoporosis: a 3-year follow-up study. J Bone Miner Metab 22:462–468
24. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, et al. (2000) Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Aging Clin Exp Res 12:1–12
25. Rizzoli R, Greenspan SL, Bone H III, Schnitzer TJ, Watts NB, Adami S, Foldes AJ, Roux C, Levine MA, Uebelhart B, Santora AC II, Kaur A, Peverly CA, Orloff JJ (2002) Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. J Bone Miner Res 17:1988–1996
26. Naruse S, Kato Y, Tani K, Hisaka A, Watanabe H, Arizono H, Taniguchi T (2004) Pharmacokinetic study of alendronate in postmenopausal Japanese women – Evaluation of urinary excretion and safety profile of alendronate after single oral administration of 35 mg and 5 mg tablet formulations (in Japanese). Rinsyo Iyaku 20:1–8
27. Greenberg RN (1984) Overview of patient compliance with medication dosing: a literature review. Clin Ther 6:592–599
28. Bone HG, Adami S, Rizzoli R, Favus M, Ross PD, Santora A, Prahalada S, Daifotis A, Orloff J, Yates J (2000) Weekly administration of alendronate: rationale and plan for clinical assessment. Clin Ther 22:15–28
29. Lanza F, Sahba B, Schwartz H, Winograd S, Torosis J, Quan H, Reyes R, Musliner T, Daifotis A, Leung A (2002) The upper GI safety and tolerability of oral alendronate at a dose of 70 milligrams once weekly: a placebo-controlled endoscopy study. Am J Gastroenterol 97:58–64
30. Greenspan S, Field-Munves E, Tonino R, Smith M, Petruschke R, Wang L, Yates J, DePapp AE, Palmisano J (2002) Tolerability of once-weekly alendronate in patients with osteoporosis: a randomized, double-blind, placebo-controlled study. Mayo Clin Proc 77: 1044–1052
31. Cryer B, Bauer DC (2002) Oral bisphosphonates and upper gastrointestinal tract problems: what is the evidence? Mayo Clin Proc 77:1031–1043
32. Simon JA, Lewiecki EM, Smith ME, Petruschke RA, Wang L, Palmisano JJ (2002) Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. Clin Ther 24:1871–1886
33. Kendler D, Kung AWC, Fuleihan GEH, Gonzalez JGG, Gaines KA, Verbruggen N, Melton ME (2004) Patients with osteoporosis prefer once weekly to once daily dosing with alendronate. Eur Menopause J 48:243–251