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Treatment of Postmenopausal Osteoporosis with Continuous Daily Oral Alendronate in Comparison with Either Placebo or Intranasal Salmon Calcitonin

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Abstract: Alendronate sodium (ALN) is a potent amino bisphosphonate which specifically inhibits osteoclastic bone resorption and has been found to reverse bone loss in several animal models. To determine if daily oral ALN treatment could prevent or reverse bone loss in osteoporotic postmenopausal women, and to compare ALN to intranasal salmon calcitonin (CT), a 2-year, double-masked, randomized, placebo-controlled study was initiated at 9 clinical centers in Italy. Two hundred and eighty six postmenopausal women (age 48–76) with spinal bone mineral density (BMD) ≥2 SD below adult mean peak, with or without vertebral crush fractures, were randomized to one of four treatment arms: ALN 10 mg daily, ALN 20 mg daily or matching placebo (these groups all double-masked), or CT 100 IU daily (open label) for 2 years. All patients received supplemental calcium (as carbonate) 500 mg daily. Bone mass was measured by dual-energy X-ray absorptiometry of the PA lumbar spine (LS) and proximal femur (femoral neck and trochanter) at 6-month intervals. Subject safety was measured through sequential clinical and laboratory evaluation. A planned 1-year interim analysis of this ongoing study was performed cetrally in a manner that maintains the double-mask for all subjects receiving oral study drug. Relative to PBO, ALN at either 10 mg or 20 mg daily increased LS BMD by 4.7% and 6.1%, respectively; each increased femoral neck BMD by 3.1% and increased trochanter BMD by 3.3% and 3.8% respectively. In contrast, CT failed to significantly increase BMD of either the spine, femoral neck or trochanter, either relative to baseline or to PBO. ALN decreased biochemical markers or bone turnover, whereas both PBO and CT were ineffective. No serious adverse experiences attributable to the use of alendronate were detected. In summary, daily oral ALN for one year appears to be effective in decreasing bone turnover and increasing bone mass at the spine and the hip. In contrast, daily CT 100 IU had no significant effects either to reduce bone turnover or to increase bone mass at either site. In conclusion, ALN effectively increased bone mass in osteoporotic menopausal women, and was associated with an excellent safety profile.

Keywords: Osteoporosis; Bisphosphonates; Alendronate; Calcitonin; Postmenopausal

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Introduction

Following menopause the rate of bone turnover increases and the amount of bone resorbed in each remodeling unit on average exceeds the amount of new bone formed. These two factors together lead to a rapid and progressive loss of bone and the development of osteoporosis, characterized by an increased fracture risk [1]. In addition, high turnover states may be associated both with more rapid loss of trabecular connectivity and with temporary weakening of trabeculae due to the presence of increased numbers of resorption cavities on trabecular bone surfaces [2–4]. For these reasons recent interest has focused on the potential use of inhibitors of bone resorption, including estrogens, calcitonins and bisphosphonates, as a means of increasing bone mineral density in patients with postmenopausal osteoporosis.

Estrogen treatment effectively prevents further bone loss, although most studies have not demonstrated sustained gains in bone mass [5]. Furthermore, poor tolerability of estrogen/progestin combinations (used to offset the increased risk of endometrial carcinoma from unopposed estrogens) and

their contraindication in a proportion of women limit the acceptability of this form of treatment [6]. Injectable calcitonins (most commonly salmon calcitonin) have poor acceptance by many patients and are only moderately effective in increasing bone mass [7]. Recently, an intranasal formulation of salmon calcitonin was introduced and has been approved in some European countries. Intranasal salmon calcitonin is well tolerated, but the efficacy of the recommended dose (100 IU/day) in increasing bone mass appears limited [8]. Thus, a clear need exists for an anti-osteoporotic therapy which is both well tolerated and more effective than intranasal salmon calcitonin.

Alendronate is a novel amino-bisphosphonate which is being investigated clinically as a potential therapeutic agent for treatment of postmenopausal osteoporosis as well as a number of other skeletal disorders associated with excessive bone resorption. It has recently received approval in Italy for the treatment of postmenopausal osteoporosis. Alendronate has been shown to be highly targeted to bone surfaces undergoing resorption, where it inhibits the action of mature osteoclasts without toxicity to these cells [9]. Alendronate either prevents bone loss or restores bone mass in several animal models of osteoporosis including ovariectomized rats and baboons [10,11]. The quality of bone formed in animals during alendronate treatment is histologically normal, without evidence of impaired mineralization even at doses 1000-fold the minimum effective anti-resorptive dose [12]. Moreover, increased bone mass in rats and baboons due to alendronate treatment was consistently associated with increased bone strength as assessed by biomechanical testing of bones ex vivo [13,14]. On the basis of these observations, increases in bone mass in patients with osteoporosis in response to alendronate treatment are predicted to increase bone strength and reduce the risk of fracture [15].

The current placebo-controlled study was designed to investigate the therapeutic efficacy, safety and tolerability of daily oral alendronate 10 or 20 mg given continuously for 2 years. An additional objective was to compare the efficacy of alendronate with that of intranasal salmon calcitonin at the most commonly prescribed dose of 100 IU/day. Results from an interim analysis of the 1-year effects of treatment are reported here. The study is continuing and will remain double-masked until the completion of the full 2-year study.

Materials and Methods

Patients

Two hundred eighty-six postmenopausal osteoporotic women aged 48–76 years were enrolled into the study. All women were at least 2 years past their natural menopause and each had a lumbar spine bone mineral density which was more than 2 SD below the reference range for young premenopausal women (<0.99 g/cm^2 for Lunar densitometers and <0.86 g/cm^2 for all other densitometer types). Evidence of previous vertebral fracture was not required as an entry criterion. Patients were excluded if they had evidence of any secondary cause of osteoporosis, other metabolic bone disease, hyper- or hypothyroidism or other health problems which could interfere with the conduct of the study or interpretation of the data. Patients were also excluded if they had received calcitonin, estrogens, progestins, anabolic steroids, glucocorticoids or high doses of vitamin D or vitamin A for more than 2 weeks within the previous months or had ever been treated with fluoride (>1 mg/day) or any bisphosphonate.

Study Design

This continuing 2-year, double-masked, placebo-controlled, randomized, parallel-group multicenter study is being conducted at nine clinical centers in Italy. The 1-year interim analysis, presented here, was conducted in a manner which preserves the double-masking for investigators and patients.

The different route of administration of the active agents being compared (oral alendronate versus intranasal salmon calcitonin) and the lack of availability of placebo for intranasal calcitonin precluded masking of the calcitonin-treated group. However, strict randomization between groups was maintained as patients had to agree to accept either masked oral therapy or open-label intranasal salmon calcitonin as determined by a defined randomization procedure. Each subject had an equal chance of being randomized to any one of four treatment groups:

1. Masked placebo to match oral alendronate
2. Masked oral alendronate 10 mg/day
3. Masked oral alendronate 20 mg/day
4. Open-label intranasal salmon calcitonin 100 IU/day (standard dose)

Patients allocated to masked oral treatment were instructed to take their single tablet of study medication with water each morning at least 1 h prior to breakfast. Salmon calcitonin was given intranasally, one puff containing 50 IU in each nostril daily. Compliance with each type of study medication was assessed throughout the study both by patient recall and, as appropriate, either by counts of returned tablets or by confirmation that returned calcitonin spray containers were empty. Patients attended two baseline visits and were seen at 3, 6, 9 and 12 months for follow-up assessments.

Alendronate tablets and matching placebo were supplied by Merck Research Laboratories, West Point, PA, USA. Intranasal salmon calcitonin spray (Calcitonina Sandoz Spray, Sandoz, Milan, Italy) was purchased locally. All patients were provided with a daily calcium supplement containing 500 mg of elemental calcium (Calcium Sandoz Forte) to be taken with the evening meal, in order to ensure that they were not calcium deficient during the study.

Bone Mass Measurements

Dual-energy X-ray absorptiometry (DXA) was used for measurement of bone mineral density (BMD) of the spine

Table 1. Summary of baseline characteristics (mean ± SD)

	Placebo	Alendronate 10 mg	Alendronate 20 mg	Intranasal calcitonin 100 IU
n	71	68	72	75
Age (yr)	59 ± 6	59 ± 6	59 ± 6	60 ± 6
Weight (kg)	60 ± 8	60 ± 7	60 ± 8	59 ± 8
Height (cm)	160 ± 6	160 ± 7	160 ± 6	159 ± 6
YSM (yr)[a]	11 ± 8	12 ± 7	11 ± 6	11 ± 6
Smokers (%)	11.3	23.5	18.1	18.7
Alcohol users (%)	2.8	8.8	6.9	6.7
Estimated calcium intake (mg/day)	546 ± 258	545 ± 264	597 ± 243	600 ± 260
Spine BMD (g/cm^2)[b]	0.73 ± 0.08	0.74 ± 0.08	0.74 ± 0.08	0.73 ± 0.08
Femoral neck BMD (g/cm^2)[b]	0.62 ± 0.07	0.63 ± 0.09	0.64 ± 0.08	0.62 ± 0.09
Trochanter BMD (g/cm^2)[b]	0.53 ± 0.08	0.53 ± 0.09	0.51 ± 0.07	0.51 ± 0.09

[a] Years since menopause.
[b] Subjects measured by Lunar densitometers ($n = 12$–16 per group) were excluded due to high values relative to other densitometer types. Lunar baseline data (not shown) were also comparable across groups.

and hip. DXA densitometers from four different manufacturers (Hologic, Waltham, MA; Lunar, Madison, WI; Norland, WI, USA; and Sophos, Paris, France) were utilized. Bone mass measurements were performed at baseline and repeated at 6 and 12 months. The primary efficacy endpoint was the percentage change from baseline in lumbar spine BMD (L1–4) and the most important secondary efficacy endpoints were the BMD changes at the femoral neck and trochanter. BMD scans were performed according to standardized procedures by trained technicians. All scans were reviewed independently without knowledge of treatment allocation by a Quality Assurance (QA) center (directed by Prof. S. Ortolani, Milan) to assess the technical adequacy of acquisition and analysis of each scan. Poorly analyzed scans were referred back from the QA center to the originating investigator site for reanalysis. Only scans which were considered technically acceptable by both the investigator site and the QA center were included in the analysis of BMD data.

Other Clinical Evaluations

Standard clinical evaluations and hematological and biochemical screening tests, including serum calcium and serum alkaline phosphatase, were performed at each study visit. Clinical and laboratory adverse experiences were documented by the clinical investigators at each follow-up visit.

Statistical Methods

An 'intention-to-treat' approach, in which all subjects with both a baseline and at least one follow-up BMD measurement were included, was used for the primary efficacy analysis. In cases where no 12-month measurement existed (e.g. due to dropout) the 6-month value was carried forward to the 12-month timepoint. All within-group tests were performed using a paired *t*-test. For between-group comparisons an overall test of treatment effect was performed on the 6-month and 12-month percentage change from baseline data using an analysis of variance (ANOVA) model with treatment and investigator as model effects. Pairwise treatment comparisons based on least-squares means were performed only if the *p*-value from the overall test for treatment effect was < 0.1. Log (percentage of baseline) was analyzed for biochemical efficacy using the same methodology as the percentage change from baseline analysis for BMD. Laboratory safety analyses were based on counts by treatment group for subjects who exceeded predefined limits of change for established

Table 2. Percentage changes from baseline in BMD of spine and hip at 12 months

	Spine		Femoral Neck		Trochanter	
	n	Mean ± SE	*n*	Mean ± SE	*n*	Mean ± SE
Placebo	67	−0.3 ± 0.65	39	−0.2 ± 0.70	39	0.2 ± 0.69
Alendronate 10 mg	64	4.4 ± 0.51**	37	2.9 ± 0.77**	37	3.5 ± 0.81**
Alendronate 20 mg	67	5.8 ± 0.54**	40	2.9 ± 0.66**	40	4.0 ± 0.87**
Calcitonin 100 IU	72	0.3 ± 0.49^{NS}	41	0.3 ± 0.72^{NS}	41	0.7 ± 0.89^{NS}

** $p < 0.01$ both versus baseline and versus placebo.
NS, not significantly different from either baseline or placebo.

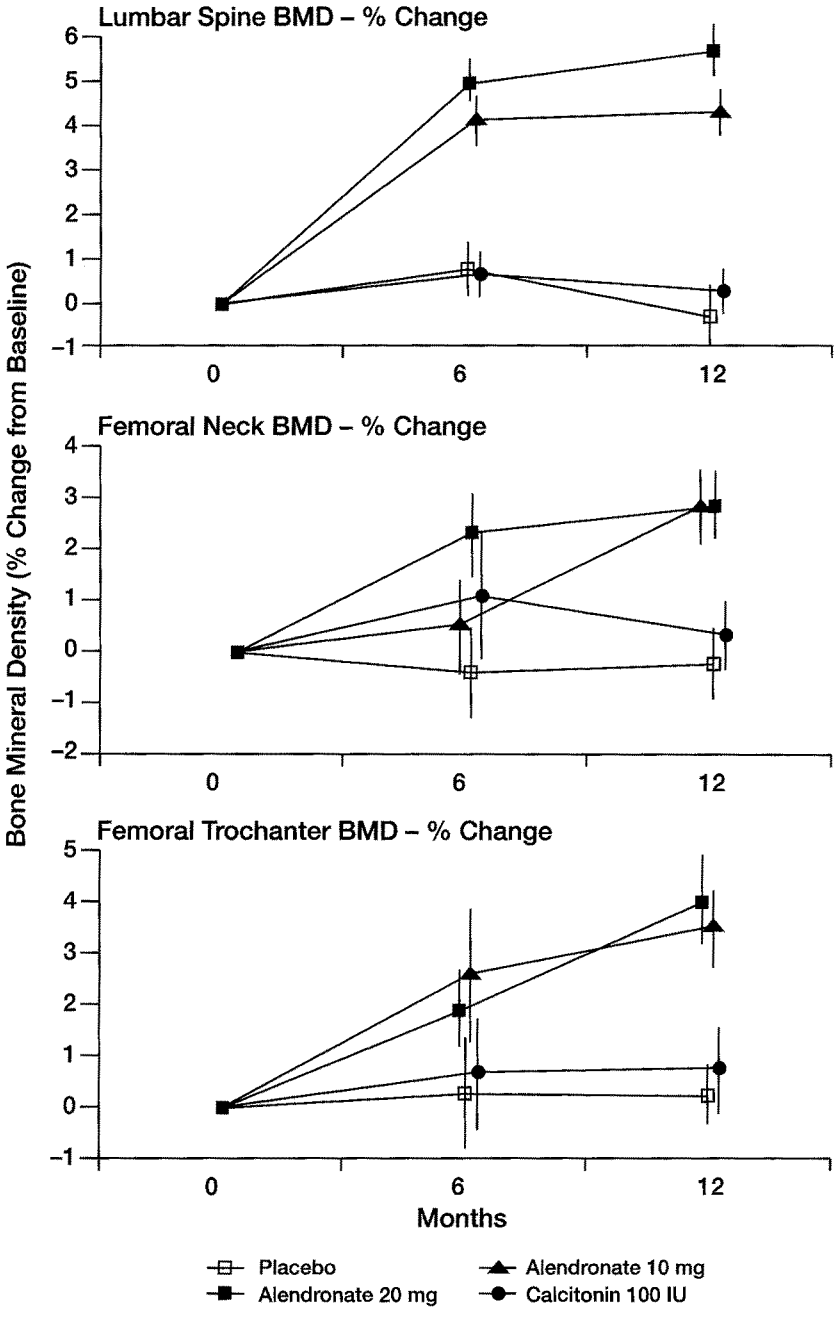

Fig. 1. Effects of alendronate 10 mg or 20 mg, intranasal salmon calcitonin or placebo on bone mineral density of the spine, femoral neck and trochanter in women with postmenopausal osteoporosis. See Table 2 for numbers per group and statistical differences.

clinically important changes in selected laboratory tests. Counts of clinical and laboratory adverse experiences were compared using Fisher's exact test. All statistical tests were two-tailed and significance was defined as $p < 0.05$.

Results

Table 1 shows several clinical and demographic patient characteristics at baseline. These characteristics, as well as family history of osteoporosis, smoking history, prevalence of ovariectomy, concomitant medications and secondary diagnoses, were comparable across treatment groups. All patients were Caucasian.

Efficacy in Increasing BMD of Spine and Hip

The mean changes from baseline BMD of the lumbar spine, femoral neck and trochanter for each treatment group are provided in Table 2 and illustrated in Fig. 1. In patients on placebo no significant changes were observed at any skeletal site. Alendronate at either 10 or 20 mg per day increased BMD of the spine, femoral neck and trochanter

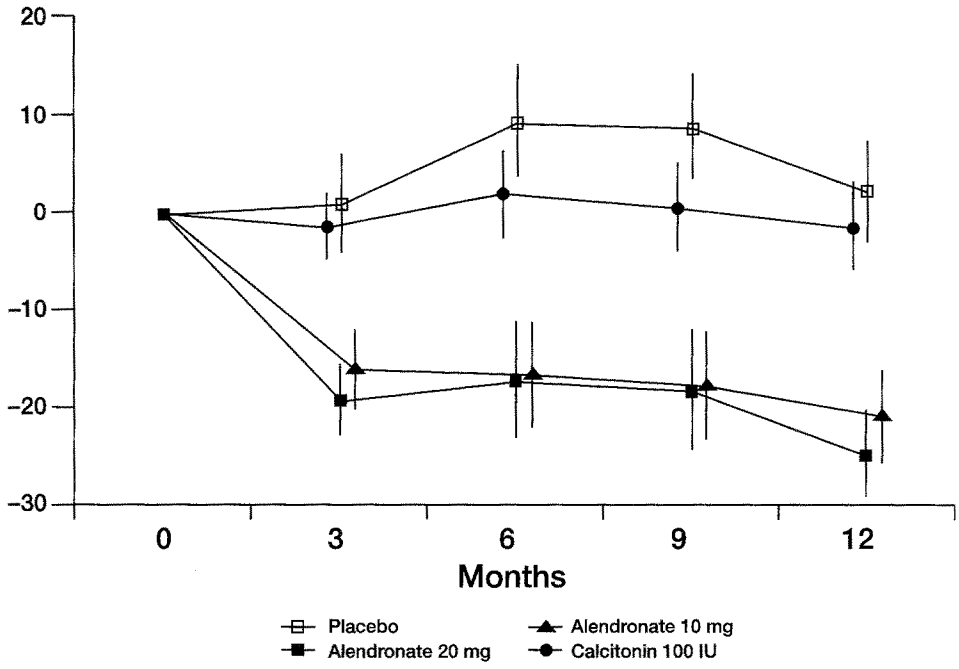

Fig. 2. Effects of alendronate 10 mg or 20 mg, intranasal salmon calcitonin or placebo on total serum alkaline phosphatase in women with postmenopausal osteoporosis. Geometric means with corresponding 90% confidence intervals are shown back-transformed from log (% of baseline) for ease of interpretation. $n = 65–73$ per group.

significantly (all $p<0.01$) with respect both to baseline and to placebo after 1 year of treatment. Relative to placebo the 10 mg and 20 mg doses increased spine BMD by 4.7% and 6.1%, respectively, each increased femoral neck BMD by 3.1%, and increased trochanter BMD by 3.3% and 3.8%, respectively, after 1 year of treatment. None of these responses differed significantly between the 10 mg and 20 mg dose groups. In marked contrast to alendronate, intranasal calcitonin failed to increase BMD of the spine, femoral neck or trochanter significantly, relative either to baseline or to placebo. At each skeletal site alendronate had a significantly greater effect in increasing BMD than did intranasal calcitonin.

Table 3. Summary of safety information

Patients	Placebo	Alendronate 10 mg/day	Alendronate 20 mg/day	Calcitonin 100 IU/day
Randomized	71	68	72	75
Any clinical AE	31	30	35	24
Upper GI AE	9	9	5	4
Drug-related AE[a]	4	8	5	8
Discontinued due to a drug-related AE	1	1	2	0
Serious AE[b]	1	0	0	1
Laboratory AE	19	25	17	22

AE, adverse experience ; GI, gastrointestinal.
[a] Considered possibly, probably or definitely drug related by the investigator.
[b] Defined as death, permanent or substantial disability, cancer, a life-threatening AE or an AE requiring hospitalization.

Biochemical Effects

Alendronate at either 10 or 20 mg per day induced a significant reduction in total serum alkaline phosphatase by month 3 to reach a new plateau level approximately 20% below baseline, indicating effective suppression of bone turnover (Fig. 2). No significant difference in the degree of suppression of alkaline phosphatase was observed between the two doses of alendronate, which were both significantly more effective than intranasal salmon calcitonin. Similarly, serum osteocalcin decreased significantly by approximately 40% at all timepoints following either dose of alendronate whereas, with the exception of the 9-month timepoint, calcitonin did not differ significantly from placebo (data not shown).

Safety

The proportions of patients with at least one clinical adverse experience (AE), either total or by each specific body system, did not differ significantly between the three masked treatment groups (Table 3). Incidences are also reported for the intranasal calcitonin group in Table 3, although statistical comparisons are not given due to the potential for some bias in the degree of AE reporting in this group because of the open nature of the therapy.

One patient in the placebo group and 1 and 2 patients in the alendronate 10 and 20 mg groups, respectively, withdrew from the study due to a clinical AE considered by the investigator to be either possibly or probably drug related. None of the AEs in alendronate-treated patients met the

definition of a serious AE (see footnote to Table 3). One serious AE occurred in each of the other two groups (cholelithiasis in a placebo-treated subject and unstable angina in a patient receiving intranasal calcitonin). The number of AEs, either total or body-system-specific, which were considered by the investigators to be possibly drug related did not differ significantly between groups. There were no significant differences between groups in the proportions of patients with an upper gastrointestinal (GI) AE. Neither were there significant differences between groups in the proportions of patients with a laboratory AE.

Discussion

Fractures at the spine and hip together account for the greater part of the morbidity and mortality observed in osteoporosis. In this study 1 year of continuous daily oral alendronate therapy induced statistically and clinically significant increases in bone mass at both the lumbar spine and hip. A number of epidemiology studies have clearly demonstrated a direct relationship between decreased bone mass and increased fracture risk [16–19]. Therefore, the increases in bone mass observed in the current study may be anticipated to reduce fracture risk and the morbidity associated with osteoporosis. The effect of alendronate in increasing hip BMD relative both to placebo and to baseline is especially noteworthy since the proximal femur is the site of the most clinically severe osteoporotic fractures. A recent study has shown that for each 1 SD decrease (approximately 10%) in hip BMD, fracture incidence at this site increased 2.6-fold [16]. Thus, assuming that the relationship between hip bone mass and fracture risk is maintained following alendronate treatment, even the 3%–4% increases in hip BMD seen in the current study would be anticipated to lead to decreases in the risk of hip fracture by approximately 20%–30%.

Of the other agents currently either available or under investigation for treatment of osteoporosis, only estrogen has been reported to prevent the loss of hip bone mass seen with placebo, but did not increase hip BMD relative to baseline [20]. No significant effects at this site have been reported following treatment with either calcitonin or with another bisphosphonate, etidronate.

Etidronate has a low potency as an anti-resorptive agent relative to alendronate [21]. The doses of etidronate required to achieve an anti-resorptive effect are the same as those that interfere with mineralization [22]. In order to avoid the risk of development of clinically significant osteomalacia during long-term treatment for osteoporosis a cyclical regimen of etidronate is required which permits completion of mineralization during a relatively long off-drug phase. Two recent studies which used an etidronate regimen consisting of 2-week cycles of etidronate repeated at 3-monthly intervals have revealed small significant increases in spine (but not hip) bone mass over 2–3 years of treatment [23,24].

A theoretical rationale for stimulation of bone resorption followed by its suppression in repeated cycles (termed ADFR) was proposed by Frost [25] as a potential mechanism for reducing the depth of resorption cavities and, thereby, allow the potential for continuous increases in bone mass [26]. This concept remains unsupported by either animal or human studies although it was the rationale for the use of oral phosphate in short cycles immediately preceding each cycle of etidronate in one of the two studies cited above [23]. However, no difference in bone mass response was noted between phosphate-treated and non-phosphate-treated patients in that study and thus the ADFR concept was not substantiated.

The action of alendronate to inhibit mature osteoclasts is almost certainly the result of the fact that these cells resorb bone at surfaces that bind a significant amount of the drug [9]. Thus, osteoclastic resorption at individual remodeling sites may be reduced. If such a reduction in bone resorption is not accompanied by a proportionate decrease in the amount of bone formed at each remodeling site, such treatment could result in long-term progressive gains in bone mass. This possibility is supported by data from a study of another bisphosphonate, pamidronate, which was given continuously for up to 4 years in osteoporotic patients [26]. These patients had progressive annual gains in spine bone mass of around 3% per year for the entire duration of treatment. Such long-term positive bone balance can be explained only by a steady-state effect of treatment to decrease bone resorption in an average remodeling unit to less than the amount of new bone formed. Studies in rats suggest that continuous dosing of alendronate may provide greater efficacy than an intermittent regimen giving the same total cumulative dose [10]. In addition to the potential for greater efficacy, continuous dosing is likely to reduce the daily dose requirements and thus reduce the potential for dose-related side effects.

Alendronate decreased both serum alkaline phosphatase and serum osteocalcin, to reach a new steady state after 3 months indicating a partial, non-cumulative inhibition of the rate of bone turnover consistent with the mechanism of action of this drug. No difference in the degree of suppression of these biochemical markers was noted between the 10 and 20 mg doses. Together with the lack of significant difference in BMD effects of these two doses this suggests that 10 mg is as effective as higher doses in decreasing bone turnover and increasing bone mass. Indeed, recent data from two other clinical trials of alendronate treatment indicate that alendronate 5 mg/day increases bone mass at the spine and hip to the same extent as doses of 10, 20 and 40 mg, whereas 1 mg did not result in significant gains in bone mass [27,28].

Alendronate doses of 10 and 20 mg were well tolerated in this study and were not associated with a significant excess of either total adverse experiences or any specific form of clinical or laboratory adverse experience relative to placebo-treated patients. As indicated above, alendronate 5 mg/day appears to be as effective as these higher doses and also demonstrates an excellent safety profile [27,28].

In this study, intranasal calcitonin had no effects on spine or hip BMD either relative to placebo or to baseline. These results are in agreement with those reported by others, who found that 100 IU/day had no significant

effect on lumbar spine density [29,30]. On the other hand, the results obtained with 200 IU of daily intranasal calcitonin are discrepant. When administered at this dose with calcium supplements the small increases observed were not consistently significant [31,32], whereas when given without calcium supplements bone density has been shown to decrease significantly more than in the placebo group [33]. Overall these findings call into question the rationale for the current widespread use of intranasal salmon calcitonin in the treatment of osteoporosis.

In conclusion, the 1-year interim data from this clinical trial clearly indicate that oral alendronate is one of the most promising therapeutic approaches for the treatment of postmenopausal osteoporosis. In contrast to intranasal salmon calcitonin, daily oral alendronate treatment over 1 year induced statistically significant and clinically important increases in bone mass of the spine and hip in women with postmenopausal osteoporosis. Alendronate at the doses tested was well tolerated and associated with a good safety profile. The gains in bone mass due to alendronate are anticipated to be associated with increased bone strength and a consequent decrease in the risk of osteoporotic fractures.

References

1. Riggs BL, Melton LJ. Involutional osteoporosis. N Engl J Med 1986;314:1676–86.
2. Parfitt AM. Age-related structural changes in trabecular and cortical bone: cellular mechanisms and biochemical consequences. Calcif Tissue Int 1984;36:123–8.
3. Riggs BL. Toward optimal therapy of established osteoporosis: evidence that antiresorptive and formation stimulating regimens reduce vertebral fractures by independent mechanisms. In: Proceedings of the fourth international symposium on osteoporosis, Hong Kong, 1993:S30.
4. Parfitt AM. Pathophysiology of bone fragility. In: Proceedings of the fourth international symposium on osteoporosis. Hong Kong, 1993:S43.
5. Lindsay R, Tohme JF. Estrogen treatment of patients with established osteoporosis. Obstet Gynecol 1990;76:290–5.
6. Ryan PJ, Harrison R, Blake GM, Fogelman I. Compliance with hormone replacement therapy (HRT) after screening for postmenopausal osteoporosis. Br J Obstet Gynaecol 1992;99:325–8.
7. Riggs BL, Melton LJ. The prevention and treatment of osteoporosis. N Engl J Med 1992;327:620–7.
8. Clissold SP, Fitton A, Chrisp A. Intranasal salmon calcitonin: a review of its pharmacological properties and potential utility in metabolism bone disorders associated with aging. Drugs Aging 1991;1:405–23.
9. Sato M, Grasser W, Endo N, et al. Bisphosphonate action: alendronate localization in rat bone and effects on osteoclast ultrastructure. J Clin Invest 1991;88:2095–105.
10. Seedor JG, Quartuccio H, Thompson DD. The bisphosphonate alendronate inhibits bone loss due to ovariectomy in rats. J Bone Miner Res 1991;6:339–46.
11. Thompson DD, Seedor JG, Quartuccio H, Solomon H, Fioravanti C, Davidson J, et al. The bisphosphonate, alendronate, prevents bone loss in ovariectomized baboons. J Bone Miner Res 1992;7:951–60.
12. Seedor JG, Balena R, Masarachia P, Rodan GA. Comparison of the therapeutic potencies of two bisphosphonates. Bone 1992;13:S116.
13. Toolan BC, Shea M, Myers ER, et al. The effect of long term alendronate on vertebral strength in ovariectomized baboons and rats. J Bone Miner Res 1991;6(Suppl 1):S248.
14. Toolan BC, Shea M, Myers ER, Borchers RE, Seedor JG, Quartuccio H, et al. Effects of 4-amino-1-hydroxybutylidene bisphosphonate on bone biomechanics in rats. J Bone Miner Res 1992;7:1399–406.
15. Black DM, Reiss TR, Karpf DB, Cummings SR. Fracture intervention trial: design and interim recruitment results. Osteoporosis Int 1993;3 (Suppl 3):S29–39.
16. Cummings SR, Black DM, Nevitt MC, Browner W, Cauley J, Ensrud K, et al. Bone density at various sites for prediction of hip fractures. Lancet 1993;341:72–4.
17. Cooper C, Wickham C, Walsh K. Appendicular skeletal status and hip fracture in the elderly: 14-year prospective data. Bone 1991;12: 361–4.
18. Hui SL, Slemenda CW, Johnston CC. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest 1988;81:1804–9.
19. Ross PD, Davis JW, Epstein RS, Wasnich RD. Preexisting fractures and bone mass predict vertebral fracture incidence in women. Ann Intern Med 1991;114:919–23.
20. Stevenson JC, Cust MP, Gangar KF, Hillard TC, Lees B, Whitehead MI. Effects of transdermal versus oral hormone replacement therapy on bone density in spine and proximal femur in postmenopausal women. Lancet 1990;335:265–9.
21. Schenk R, Eggli P, Fleisch H, Rosini S. Quantitative morphometric evaluation of the inhibitory activity of new aminobisphosphonates on bone resorption in the rat. Calcif Tissue Int 1986;38:342–9.
22. Boyce BF, Smith R, Fogelman I, Johnston E, Ralston S, Boyle IT. Focal osteomalacia due to low-dose diphosphonate therapy in Paget's disease. Lancet 1984;11:821–4.
23. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990;323:73–9.
24. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;5: 183–92.
25. Frost HM. Treatment of osteoporosis by manipulation of coherent bone cell populations. Clin Orthop 1979;143:227–44.
26. Valkema R, Vismans FJFE, Papapoulos SE, Powels EKJ, Bijvoet OLM. Maintained improvement in calcium balance and bone mineral content in patients with osteoporosis treated with the bisphosphonate APD. Bone Miner 1989;5:183–92.
27. Santora AC, Bell NH, Chesnut CH, Ensrud K, Genant HK, Grimm R, et al. Oral alendronate treatment of bone loss in postmenopausal osteopenic women. [abstract] J Bone Miner Res 1993;8(Suppl 1):S131.
28. McClung MR, Yates AJ. Alendronate prevents or reverses bone loss at the spine and hip in recently menopausal women. [abstract] J Bone Miner Res 1993;8(Suppl 1):S141.
29. Thamsborg G, Storm TL, Sykulski R, Brinch E, Nielsen HK, Sørensen OH. Effect of different doses of nasal salmon calcitonin on bone mass. Calcif Tissue Int 1991;48:302–7.
30. Overgaard K, Hansen MA, Jensen SB, Christiansen C. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose–response study. BMJ 1992;305: 556–61.
31. Overgaard K, Riis BJ, Christiansen C, Pødenphant J, Johansen JS. Nasal calcitonin for treatment of established osteoporosis. Clin Endocrinol 1989;30:435–42.
32. Overgaard K, Hansen MS, Heiss Nielsen VA, Riis BJ, Christiansen C. Discontinuous calcitonin treatment of established osteoporosis: effects of withdrawal of treatment. Am J Med 1990;89:1–6.
33. Meunier PJ, Gozzo I, Chaumet-Riffaud PD, Delmas PD, Guignard M, Chapuy MC, Duboeuf F. Dose–effect on bone density and parathyroid function of intranasal salmon calcitonin when administered without calcium in postmenopausal women. [abstract]. J Bone Miner Res 1992;7(Suppl 1):abst.950.