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Effects of Oral Ibandronate Administered Daily or Intermittently on Fracture Risk in Postmenopausal Osteoporosis

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ABSTRACT: Oral daily (2.5 mg) and intermittent ibandronate (between-dose interval of >2 months), delivering a similar cumulative exposure, were evaluated in 2946 osteoporotic women with prevalent vertebral fracture. Significant reduction in incident vertebral fracture risk by 62% and 50%, respectively, was shown after 3 years. This is the first study to prospectively show antifracture efficacy for the intermittent administration of a bisphosphonate.

Introduction: Bisphosphonates are important therapeutics in postmenopausal osteoporosis. However, they are currently associated with stringent dosing instructions that may impair patient compliance and hence therapeutic efficacy. Less frequent, intermittent administration may help to overcome these deficiencies. This study assessed the efficacy and safety of oral ibandronate administered either daily or intermittently with a dose-free interval of >2 months.

Materials and Methods: This randomized, double-blind, placebo-controlled, parallel-group study enrolled 2946 postmenopausal women with a BMD T score ≤ -2.0 at the lumbar spine in at least one vertebra (L_1–L_4) and one to four prevalent vertebral fractures (T_4–L_4). Patients received placebo or oral ibandronate administered either daily (2.5 mg) or intermittently (20 mg every other day for 12 doses every 3 months).

Results and Conclusions: After 3 years, the rate of new vertebral fractures was significantly reduced in patients receiving oral daily (4.7%) and intermittent ibandronate (4.9%), relative to placebo (9.6%). Thus, daily and intermittent oral ibandronate significantly reduced the risk of new morphometric vertebral fractures by 62% ($p = 0.0001$) and 50% ($p = 0.0006$), respectively, versus placebo. Both treatment groups also produced a statistically significant relative risk reduction in clinical vertebral fractures (49% and 48% for daily and intermittent ibandronate, respectively). Significant and progressive increases in lumbar spine (6.5%, 5.7%, and 1.3% for daily ibandronate, intermittent ibandronate, and placebo, respectively, at 3 years) and hip BMD, normalization of bone turnover, and significantly less height loss than in the placebo group were also observed for both ibandronate regimens. The overall population was at low risk for osteoporotic fractures. Consequently, the incidence of nonvertebral fractures was similar between the ibandronate and placebo groups after 3 years (9.1%, 8.9%, and 8.2% in the daily, intermittent, and placebo groups, respectively; difference between arms not significant). However, findings from a posthoc analysis showed that the daily regimen reduces the risk of nonvertebral fractures (69%; $p = 0.012$) in a higher-risk subgroup (femoral neck BMD T score < -3.0). In addition, oral ibandronate was well tolerated. Oral ibandronate, whether administered daily or intermittently with an extended between-dose interval of >2 months, is highly effective in reducing the incidence of osteoporotic fractures in postmenopausal women. This is the first time that significant fracture efficacy has been prospectively shown with an intermittently administered bisphosphonate in the overall study population of a randomized, controlled clinical trial. Thus, oral ibandronate holds promise as an effective and convenient alternative to current bisphosphonate therapies.

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Key words: osteoporosis, bisphosphonates, ibandronate, vertebral fracture

INTRODUCTION

Approximately one-third to one-half of women will sustain at least one osteoporotic fracture during their lifetime.[1,2] Hence, this debilitating condition, with its significant burden of morbidity and mortality, has important implications for public health.[3] Bisphosphonates are im-

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portant agents in the treatment of postmenopausal osteoporosis (PMO).[4] Bisphosphonates exert their therapeutic effect by reducing osteoclast-mediated bone resorption,[4] which results in a decrease in bone turnover, an increase in BMD, and a reduction in fracture risk.[5–8]

Despite proven efficacy, regular administration of nitrogen-containing bisphosphonates is known to cause gastrointestinal (GI) adverse events in some patients.[9,10] In addition, all oral bisphosphonates are associated with relatively low intestinal absorption,[9,11] which is potentially further reduced by concomitant intake of food or drink (other than water).[11,12] To ensure GI tolerability and maximize bioavailability, patients taking oral bisphosphonates must adhere to relatively stringent dosing guidelines that, depending on dosing frequency, may be inconvenient to some patients and may impair long-term compliance. A recent large retrospective analysis has shown that poor adherence to osteoporosis therapies is likely to potentially jeopardize efficacy.[13] Less frequent, intermittent dosing schedules are expected to increase patient convenience[14–16] and thereby promote long-term adherence to therapy and potentially optimize therapeutic outcomes in PMO.

Ibandronate is a highly potent nitrogen-containing bisphosphonate[17] that has the potential to be administered intermittently with extended between-dose intervals. Preclinical studies conducted in rats, dogs, and monkeys have investigated intermittent treatment with ibandronate[18–20] and have shown that daily and intermittent regimens produce equivalent benefits in reversing bone loss, increasing bone strength, and restoring or preventing loss of normal bone architecture.[18,19]

These findings were further supported by phase II clinical studies of ibandronate administered both daily and intermittently.[21–24] A recent double-blind, placebo-controlled study compared the efficacy and safety of daily (2.5 mg) versus intermittent (20 mg ibandronate every other day for 12 doses every 3 months) oral ibandronate therapy in women with PMO.[23] This study found both regimens to produce significant and similar increases in lumbar spine and hip BMD and suppression of bone turnover. Both daily and intermittent ibandronate were well tolerated.

Based on these positive results, a phase III fracture study, oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE), was conducted to investigate the efficacy and safety of oral ibandronate administered daily or intermittently with a between-dose interval of >2 months in women with PMO. A principal intention of this study was to investigate whether intermittent ibandronate regimens with extended between-dose intervals can reduce the risk of vertebral fractures.

MATERIALS AND METHODS

Participants

Patients were screened for eligibility at 73 centers in Europe and North America. Eligible patients were 55–80 years of age and ≥5 years postmenopausal, with one to four prevalent vertebral fractures (T_4–L_4) and a BMD T score of −2.0 to −5.0 in at least one vertebra (L_1–$L4_)$. Patients with upper GI disorders or taking medication with a potential for GI irritation were not specifically excluded. The main exclusion criteria were a BMD T score of < −5.0 at the lumbar spine; more than two prevalent fractures of the lumbar spine; diseases, disorders, or therapy (within the last 6 months) known to affect bone metabolism; previous treatment with bisphosphonates; fluoride treatment within the last 12 months or for a total duration of >2 years; renal impairment (serum creatinine >2.4 mg/dl [>212 μM]); contraindications to calcium or vitamin D therapy; and hyper- or hypocalcemia. The Institutional Review Boards of the participating centers approved the study, and all patients provided written informed consent.

Treatment

The method of block randomization was used in this 3-year multicenter, double-blind, placebo-controlled, parallel-group antifracture study. Patients were randomized in blocks of six to treatment with either continuous oral ibandronate (2.5 mg daily), intermittent oral ibandronate at a similar total dose (20 mg every other day for 12 doses every 3 months), or placebo. Patients assigned to the intermittent regimen received placebo tablets on the days without active treatment. Participants were instructed to take their tablets immediately after rising and 1 h before food, nonstudy medications, and fluids other than plain water. All participants received daily calcium (500 mg) and vitamin D (400 IU) supplementation.

Outcomes

Patients underwent a screening visit within 3 months before the start of the study. Baseline information (apart from the X-rays for fracture assessment, which had been undertaken during the screening phase) was collected at the same time that study medication was initially dispensed. Subsequent visits took place at 3-month intervals.

The primary endpoint was the rate of patients with new morphometric vertebral fractures at 3 years of treatment with the study medication. Secondary efficacy measures included the rate of patients with new or worsening vertebral fractures, clinical vertebral fractures, and clinical osteoporotic nonvertebral fractures; relative changes in BMD at the lumbar spine and proximal femur (including subregions); relative changes in biochemical markers of bone turnover; and changes in height (measured using a stadiometer). With regards to safety, adverse events, parameters of renal and liver function, serum electrolyte concentrations, and blood counts were assessed during the study.

Prevalent and incident vertebral fractures: Lateral radiographs of the thoracic and lumbar spine were performed at the screening visit to determine the presence of prevalent fractures using well-established standardized techniques.[25–27] Thereafter, lateral radiographs of the spine were performed annually for assessment of incident fractures. The diagnosis of fractures was based on morphometric criteria and was further confirmed by qualitative assessment of radiologists at one of two independent central reading facilities. Morphological diagnosis of a new vertebral fracture required a relative height reduction of at least 20% and an absolute decrease of at least 4 mm in any vertebral body height from the baseline radiograph.

Clinical fractures: All clinical vertebral and nonvertebral fractures were identified symptomatically and reported as adverse events by the investigator. Suspected clinical fractures were radiographically confirmed. Non-osteoporotic fractures (fractures of the hands, feet, face, and skull) were excluded from all subsequent analyses.

BMD: BMD measurements were performed every 6 months during the first 2 years and again at the final visit using DXA (Hologic QDR and Lunar scanners). Measurements were made at the lumbar spine (L_2–L_4) and proximal femur. All measurements underwent quality assurance and longitudinal correction at one of two independent central sites. T scores at the hip were derived from the third National Health and Nutrition Examination Survey (NHANES III) database. Measurements were also taken at the distal forearm in a subset of patients.

Biochemical markers of bone turnover: Urinary excretion of C-telopeptide of the α-chain of type I collagen (CTX/creatinine),[28] urinary excretion of N-telopeptide of the α-chain of type I collagen (NTX/creatinine),[29] serum osteocalcin concentration,[30] and serum concentration of bone-specific alkaline phosphatase (BSAP)[31] were measured in ~20% of the total study population at selected investigational sites. Assessments of biochemical markers of bone turnover were undertaken at 3-month intervals during the first 6 months, thereafter at 6-month intervals until the end of the second year, and then at the final visit.

Planned sample size

The sample size was based on a clinically relevant difference of 40% in the incidence of new vertebral fractures between placebo and active treatment. For the study to achieve a power of at least 90%, >2040 patients were required to complete the first year for the final intent-to-treat (ITT) analysis. To allow for patient withdrawals, the intention was to enroll 2400 patients. However, because of the multicenter organization of the study, it was difficult to prevent further recruitment immediately after the target number was reached. Thus, the protocol was amended to allow inclusion of additional patients.

Statistical methods

The ITT population comprised all patients who received at least one dose of study medication and who attended at least one follow-up visit. The ITT population was used for all fracture analyses (including height). All safety analyses were performed on the same group of patients as the ITT population. As predefined in the protocol, analyses of all nonfracture efficacy endpoints were performed based on the per-protocol population, which was defined to assess the efficacy of ibandronate in a cohort with ideal study conditions. This population included all patients in the ITT population, except those with a protocol deviation deemed to have a significant impact on the efficacy variables (i.e., major deviations regarding the inclusion/exclusion criteria, patients with insufficient compliance [<75% of the study medication], documentation of forbidden concomitant medication that could bias the BMD/fracture results, and patients lacking an assessable baseline and follow-up for both BMD and X-ray assessments).

The primary endpoint, the rate of patients with new morphometric vertebral fractures at 3 years, was analyzed by testing the homogeneity between treatment groups of the time-to-event curves, the event being the first new incident vertebral fracture. The single vertebra BMD inclusion criterion resulted in the inclusion of almost 20% of patients with a mean lumbar spine (L_2–L_4) BMD T score above −2.0. To control for possible inhomogeneities between treatment groups with respect to a baseline BMD T score above and below −2.0, the data analysis plan prespecified testing for an eventual interaction between these groups. Because a statistically significant interaction was discovered after data unblinding, in the primary analysis, the treatment-effect size was estimated as the relative risk reduction of the first new incident vertebral fracture calculated by a Cox regression model including the interaction term. Estimates of treatment effects after 1 and 2 years were derived using the same model.

For clinical vertebral fractures and other clinical fractures, the incidences were derived from Kaplan-Meier time-to-event analyses. For the BMD measurements, the statistical comparison of treatment groups was based on the 3-year visit. An ANOVA analysis was used for the comparison of all treatment groups based on relative changes in the per-protocol population. The average changes in height per year were compared among treatment groups using a suitable analysis of covariance model.

RESULTS

Patient disposition and baseline characteristics

The study took place between 1 October 1996 and 8 December 2000. After screening 18,447 patients, 2946 were enrolled and randomized, with 982 patients in each of the three treatment groups (Fig. 1). Of the 2946 patients randomized to therapy, 1938 completed treatment. The number of completers was slightly higher in the ibandronate groups than in the placebo group. In addition, the number of patients completing (64–68%) the study was similar to well-designed trials with other bisphosphonates.[7] For those patients that did not complete the study, the mean duration time was 2.42, 2.48, and 2.46 years for those receiving placebo, daily ibandronate, and intermittent ibandronate, respectively. The ITT and safety populations comprised a total of 2929 patients, whereas 2125 patients were evaluable for the per-protocol analyses.

Baseline values and demographic characteristics were well balanced between treatment groups and are summarized in Table 1.

The number of patients taking concomitant medications, such as nonsteroidal anti-inflammatory agents (NSAIDs) and antacids were similar between the groups (35–37% and 61–63% for NSAIDs and antacids, respectively). Similarly, the number of patients with pre-existing GI disorders was comparable across the treatment arms (25–28%). Serious upper GI conditions, such as peptic ulcer, were uncommon (≤1%).

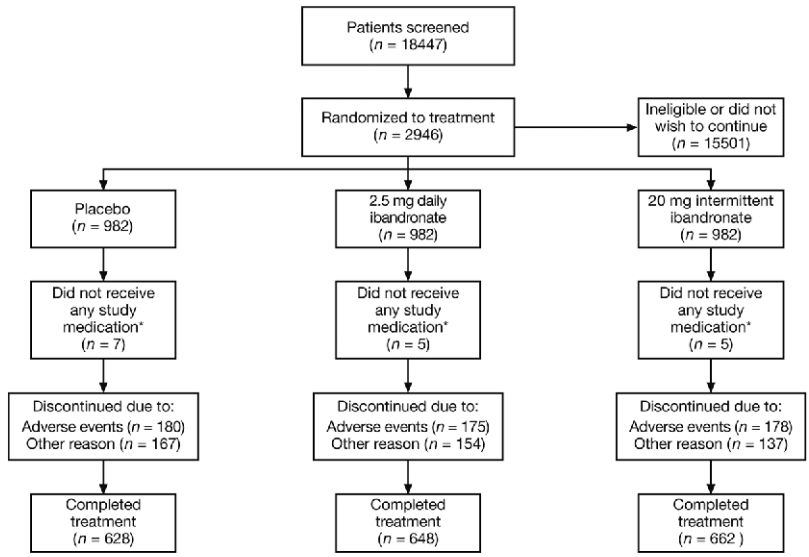

FIG. 1. Patient disposition during the study.

TABLE 1. SUMMARY OF BASELINE CHARACTERISTICS

	Placebo (n = *975*)	*Ibandronate (2.5 mg daily;* n = *977*)	*Ibandronate (20 mg intermittent;* n = *977*)
Age (years*)	69 (6)	69 (6)	69 (6)
Height (cm)	160 (6)	160 (6)	160 (6)
Weight (kg)	67 (11)	67 (11)	67 (11)
Time since menopause (years)	20.8 (7.8)	20.9 (8.0)	20.8 (8.0)
Patients with one fracture	906 (93%)	920 (94%)	917 (94%)
Patients with two fractures	421 (43%)	433 (44%)	413 (42%)
Lumbar spine BMD (T score)	−2.8 (0.9)	−2.8 (0.9)	−2.7 (0.9)
Femoral neck BMD (T score)	−2.0 (0.9)	−2.0 (0.9)	−2.0 (0.9)
Total hip BMD (T score)*	−1.7 (0.9)	−1.7 (0.8)	−1.7 (0.9)
Performed in selected centers only	(*n* = 224)	(*n* = 223)	(*n* = 229)
CTX/creatinine (g/mol)	0.25 (0.12)	0.26 (0.14)	0.26 (0.12)
NTX/creatinine (nmol/mmol)	61.23 (33.93)	64.63 (40.35)	63.59 (32.38)
Serum osteocalcin (ng/ml)	19.68 (7.71)	19.08 (9.25)	20.36 (9.38)
Serum BSAP (U/liter)	40.93 (18.24)	44.42 (20.70)	44.54 (19.03)

Values are mean (SD).
* NHANES adjusted.

Efficacy

New vertebral fracture: A total of 149 patients in the ITT population suffered at least one new vertebral fracture during the trial: 73 patients in the placebo group compared with 37 and 39 patients in the daily and intermittent ibandronate groups, respectively. By life-table analysis, the rate of patients with new incident vertebral fractures at year 3 was estimated to be 9.6% (95% CI, 7.5–11.7) for the placebo group and 4.7% (95% CI, 3.2–6.2) and 4.9% (95% CI, 3.4–6.4) for the daily and intermittent ibandronate groups, respectively. The relative risk reductions compared with placebo were 62% ($p = 0.0001$; 95% CI: 41–75) and 50% ($p = 0.0006$; 95% CI: 26–66) for the daily and intermittent groups, respectively, after 3 years (Fig. 2) for the prespecified primary analysis using the adjusted Cox regression analysis. In a secondary analysis without correction for the statistically significant interaction, daily and intermittent ibandronate reduced the risk of incident new vertebral fractures by 52% ($p = 0.0001$; 95% CI: 28–68) and 50% ($p = 0.0006$; 95% CI: 26–66), respectively. The difference in relative risk between the two active treatment groups was not statistically significant ($p = 0.28$). Similar and significant reductions in the relative risk for new vertebral fractures were observed after 2 years (61% [$p = 0.0006$; 95% CI: 33–77] and 56% [$p = 0.0017$; 95% CI: 27–74] in the daily and intermittent groups, respectively). After the first year, the relative risk for new vertebral fractures was reduced by 58% (95% CI: −2 to 83) in the daily ibandronate group; however, this reduction missed statistical significance ($p = 0.0561$). After 3 years, significant reductions in

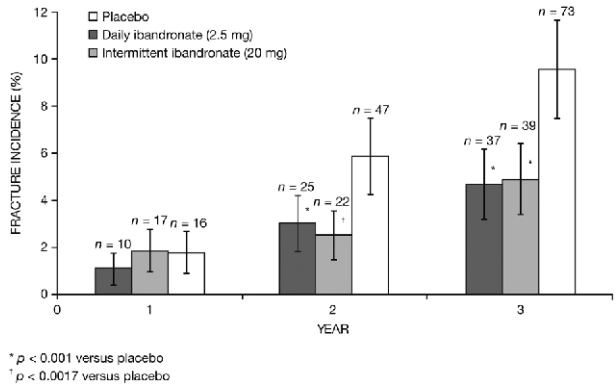

FIG. 2. Cumulative effect of oral daily and intermittent ibandronate on new vertebral fractures during each year of study.

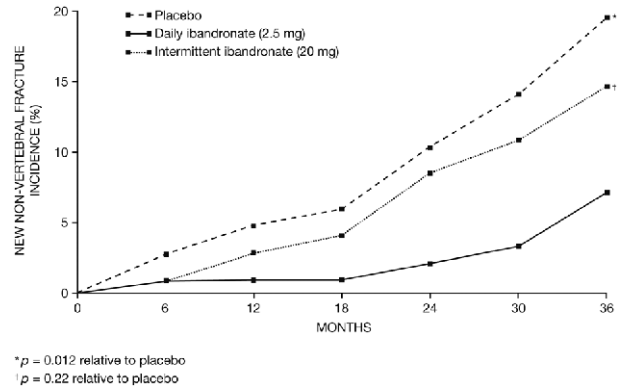

FIG. 3. Effect of oral daily and intermittent ibandronate on clinical nonvertebral fractures in patients with low femoral neck BMD (T score < -3).

the risk of new or worsening vertebral fractures were observed with both the 2.5 mg daily and 20 mg intermittent treatment groups (62% [$p = 0.0001$; 95% CI: 43–75] and 50% [$p = 0.0005$; 95% CI: 26–65], respectively).

Clinical vertebral fractures: A total of 85 patients in the ITT population reported symptoms that were ultimately confirmed to be caused by a new clinical vertebral fracture: 41 of these patients were in the placebo group and 22 each were in the daily and intermittent ibandronate groups. The estimated incidence rates were 5.3% (95% CI: 3.7–6.9) in the placebo group versus 2.8% (95% CI: 1.6–3.9) and 2.8% (95% CI: 1.6–3.9) in the daily and intermittent groups, respectively. The differences in treatment effect between the oral ibandronate treatment groups and placebo were statistically significant ($p = 0.0117$ for 2.5 mg and $p = 0.0143$ for 20 mg), with a relative risk reduction of 49% for the 2.5 mg group and 48% for the 20 mg intermittent group.

Clinical osteoporotic nonvertebral fractures: The incidence of clinical nonvertebral fractures was low and similar between the placebo and active treatment groups (8.2%, 9.1%, and 8.9% in the placebo, 2.5 mg ibandronate, and 20 mg ibandronate groups, respectively). The study population had a relatively high mean BMD at the proximal femur (total hip [mean T score $= -1.73$], femoral neck [mean T score $= -2.03$]) at baseline compared with other phase III clinical trials in PMO,[7,32–36] and therefore was at relatively low risk for new nonvertebral fractures.

The effect of ibandronate on the risk of nonvertebral fracture depended on baseline BMD at the femoral neck. A significant interaction was found between treatment effect on nonvertebral fractures and a femoral neck baseline BMD above and below a T score of -3.0 ($p = 0.0027$). Further analysis showed a relative risk reduction of nonvertebral fractures with oral daily and intermittent oral ibandronate (69% [$p = 0.013$] and 37% [$p = 0.22$], respectively) in patients with a baseline femoral neck BMD T score < -3.0 (Fig. 3).

Height loss: Height of the patients was assessed at each visit. After 3 years of treatment, a mean stature loss of 5.6 mm was observed for patients receiving placebo, which was significantly more extensive than the loss observed in patients receiving 2.5 (3.9 mm, $p = 0.0005$) or 20 mg (4.7 mm, $p = 0.0144$) ibandronate, respectively.

BMD: After 3 years of treatment, oral ibandronate was associated with statistically significant and progressive increases in BMD at the lumbar spine and hip (total hip, femoral neck, and trochanter) compared with placebo (Fig. 4). Relative to baseline, BMD at the lumbar spine increased by 1.3%, 6.5%, and 5.7% in the placebo, daily, and intermittent groups, respectively, after 36 months ($p < 0.0001$ for each ibandronate group versus placebo; Fig. 4A). At the total hip, after 3 years, BMD increased by 3.4% and 2.9% with daily and intermittent ibandronate, respectively, compared with a loss of 0.7% in the placebo group ($p < 0.0001$ for each ibandronate group versus placebo; Fig. 4B). Similar findings of BMD gains relative to baseline were obtained for the femoral neck (2.8% and 2.4% versus -0.6% in the daily and intermittent ibandronate groups versus placebo, respectively; Fig. 4C) and the trochanter (5.5% and 5.2% versus 0.2%, respectively; Fig. 4D) and for all these sites after 6 months, 1 year, and 2 years.

Treatment with both ibandronate regimens increased BMD at all the forearm sites (global distal forearm, total wrist, distal radius and ulna, and ultradistal radius), relative to placebo, with the exception of the ultradistal radius in the daily treatment group. However, because of the small number of patients analyzed, meaningful statistical comparisons could not be made.

Biochemical markers of bone turnover: Both ibandronate regimens were associated with substantial, significant, and sustained reductions in biochemical markers of bone turnover. After just 3 months, there was a highly pronounced reduction in biochemical markers of bone resorption (CTX/creatinine and NTX/creatinine) and formation (serum osteocalcin and BSAP) in both ibandronate treatment groups versus baseline and placebo, which was sustained throughout the rest of the study ($p < 0.0001$ for all bone markers versus placebo after 3 years). The magnitude of reduction in biochemical markers of bone turnover levels was comparable between regimens. These data will be the subject of a separately communicated analysis.

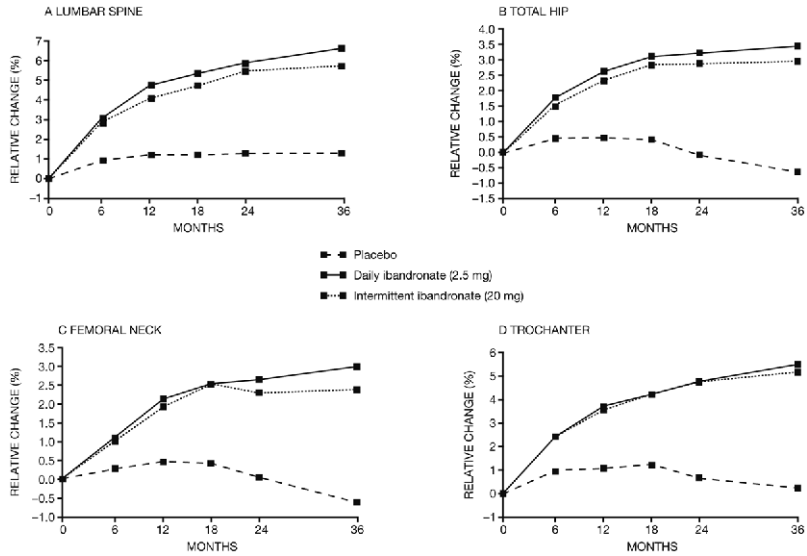

FIG. 4. Mean relative change from baseline in BMD at the (A) lumbar spine, (B) total hip, (C) femoral neck, and (D) trochanter over 3 years (per protocol population; $p < 0.0001$ for difference between both ibandronate groups vs. placebo at all sites after 3 years).

TABLE 2. OVERALL SUMMARY OF SAFETY (%)

	Placebo (n = *975*)	*Daily ibandronate (2.5 mg,* n = *977)*	*Intermittent ibandronate (20 mg,* n = *977)*
Any adverse event	88.9	90.9	91.9
Any drug-related adverse events	17.9	19.8	18.5
Any serious adverse event	21.6	24.0	25.3
Any drug-related serious adverse event	0.3	0.3	0.7
Any adverse event leading to withdrawal from study treatment	18.8	18.5	18.5
Any drug-related adverse event leading to withdrawal from study treatment	8.1	7.5	7.2
Any adverse event leading to death	1.0	1.1	0.8

Safety: Both regimens of oral ibandronate were well tolerated, with an incidence of adverse events similar to placebo. No statistically significant differences between study arms were found in the overall incidence of adverse events, the incidence of adverse events considered by the investigator to be drug-related, or the incidence of drug-related adverse events resulting in withdrawal from the study (Table 2). Similarly, the numbers of serious adverse events, overall withdrawals caused by adverse events, and deaths were also well balanced between the three groups.

Of note, the frequency of upper GI adverse events was comparable in the placebo, daily ibandronate, and intermittent ibandronate study arms (Table 3), despite the lack of strict GI exclusion criteria (~30% of patients had a history of GI disorders). Although dyspepsia was reported with slightly higher frequency in patients treated with daily ibandronate 2.5 mg (11% compared with 9% for placebo and 9% for intermittent ibandronate 20 mg), this increase was not significant ($p > 0.08$). Subgroup analyses of patients with and without a history of GI disorders showed that oral ibandronate did not increase the overall risk of upper digestive system adverse events compared with placebo in patients with such a history (data not shown). In addition, among aspirin or NSAID users, the incidence of upper GI adverse events in patients treated with ibandronate 2.5 mg daily and ibandronate 20 mg intermittently was similar to that seen in placebo-treated patients (data not shown).

TABLE 3. SUMMARY OF UPPER GASTROINTESTINAL ADVERSE EVENTS (%)

Adverse events	*Placebo* (n = *975)*	*Ibandronate (2.5 mg daily,* n = *977)*	*Ibandronate (20 mg intermittent,* n = *977)*
Duodenal ulcer	0.9	0.1	0.1
Dyspepsia	9.1	11.4	9.0
Belching	0.2	0.4	0.5
Gastritis	2.2	2.3	1.2
Gastroenteritis	5.5	5.5	6.3
GI pain*	2.6	1.9	2.5
Nausea	6.3	4.2	6.4
Oesophageal ulcer	0.1	0.2	0.1
Oesophageal stenosis	0.1	0.2	0.0
Oesophagitis	1.0	1.5	1.0
Stomach ulcer	0.6	0.3	0.5
Vomiting	2.5	3.0	2.8

* GI pain includes chest pain defined as being of abdominal origin.

No clinically relevant changes in laboratory parameters were observed, and the distribution of marked laboratory abnormalities was balanced between treatment groups.

DISCUSSION

In the current placebo-controlled study, oral ibandronate was administered either daily (2.5 mg) or intermittently (20 mg every other day for 12 doses every 3 months) at a similar cumulative dose. Both daily and intermittent oral ibandronate were highly effective in reducing the incidence of new vertebral fractures, with a sustained effect over 3 years. At the end of the study, the daily and intermittent treatment groups reduced the risk of new morphometric vertebral fractures by 62% ($p = 0.0001$) and 50% ($p = 0.0006$), respectively, compared with placebo. After 3 years, both regimens of ibandronate also produced a statistically significant reduction in new or worsening vertebral fractures and clinical vertebral fractures.

Although it is difficult to compare across different studies, the point estimate of the relative risk reduction of new vertebral fractures seen with 2.5 mg oral daily ibandronate is the highest sustained reduction in vertebral fracture risk observed among current bisphosphonates.[7,32–36] After 3 years, the relative risk reduction in new vertebral fractures observed with oral daily alendronate (5–10 mg) and risedronate (5 mg) in phase III pivotal trials was up to 50%[33] and 49%,[36] respectively, compared with 62% and 50% with oral daily and intermittent ibandronate, respectively. Single studies comparing the effects of these different bisphosphonates on fracture rates will be needed to confirm these findings.

Furthermore, although extended dosing intervals have been studied with other bisphosphonates,[37–40] ibandronate is the first to prospectively show robust antifracture efficacy with a between-dose interval of >2 months in the overall population of an adequate and well-controlled clinical trial. Etidronate, a non–nitrogen-containing bisphosphonate, is administered with an extended between-dose interval and is widely used to treat PMO in Europe. However, reduction in fracture risk has only been shown with etidronate in a subgroup population (or with phosphate)[5] and when data are excluded from analysis.[41] Consequently, etidronate has failed to produce significant and robust vertebral fracture benefit in the overall population of a large well-designed prospective trial.

In the study reported here, no statistically significant reduction was seen in nonvertebral fractures in the overall population. However, on average, patients had a relatively high proximal femur BMD at baseline compared with similar phase III fracture prevention trials of other bisphosphonates.[6,7,32–36] For example, in this study, mean BMD at the femoral neck (0.63–0.64 g/cm^2) was almost 10% higher compared with that seen in the Fracture Intervention Trial 1 (FIT1; 0.56 g/cm^2).[6] Furthermore, the actual fracture risk of the populations within these studies can be quantitatively derived from the incidence of new vertebral fractures in the placebo groups. A comparison of the fracture incidence in the placebo groups of BONE and FIT1 (9.6% and 15.0% after 3 years, respectively) shows that the population of the BONE study was at considerably lower risk of fractures than the population in the FIT1 study. However, in a posthoc analysis, oral daily ibandronate significantly reduced the risk of nonvertebral fractures in a subgroup of the overall population (women with a BMD T score at the femoral neck of < -3.0). In this higher-risk subgroup, oral daily ibandronate reduced the incidence of nonvertebral fractures by 69% ($p = 0.013$) relative to placebo. Although this is a retrospective analysis, and therefore its interpretation should be treated with caution, this study was well designed and conducted in a large number of patients. Consequently, it is likely that these findings will be relevant to the clinical setting.

In tandem with these significant reductions in vertebral and nonvertebral fractures (in a high-risk subgroup), both daily and intermittent ibandronate were associated with similar statistically significant increases in lumbar spine and hip (total hip, femoral neck, and trochanter) BMD and suppression of biochemical markers of bone turnover versus placebo. Notably, after 1 year, the lumbar spine BMD gains observed with oral daily and intermittent ibandronate are similar to those noted in a randomized, double-blind, placebo-controlled trial investigating an intermittent intravenous regimen of ibandronate (2 mg), given by injection once every 3 months (5.0% with the 2 mg intravenous regimen versus 4.7% and 4.0% in the oral daily and intermittent arms).[42] In contrast, however, the spinal BMD increases seen with oral ibandronate in our study are substantially greater than those observed with lower 3-month doses of intravenous ibandronate (0.5 and 1 mg), which produced suboptimal efficacy.[43] The optimal dosing schedule of intermittent intravenous ibandronate injections is currently being investigated in a large phase II/III trial.

Oral daily ibandronate and intermittent ibandronate were well tolerated, with a safety profile similar to placebo. There was no association between ibandronate treatment and an increased risk of upper GI adverse events, despite the fact that patients with a history of such complaints were not specifically excluded from the study. Notably, rates of upper GI adverse events were similar for both ibandronate regimens and placebo in patients with a history of upper GI disease and patients using NSAIDs or aspirin. This study shows the substantial antifracture efficacy and excellent tolerability of daily and intermittent ibandronate dosing regimens. As a result, oral ibandronate has the potential to become an important alternative to currently licensed treatments for PMO. The robust results from this study verify the concept that intermittent treatment with ibandronate given with extended between-dose intervals can reduce fracture risk, and these findings are assisting in identifying novel intermittent ibandronate regimens. Current oral bisphosphonates are associated with inconvenient dosing guidelines that must be adhered to on a frequent basis (daily or weekly). The innovative, simplified dosing regimens of ibandronate in development (oral monthly and intermittent intravenous injections) will offer greater convenience, while ensuring lasting efficacy and good tolerability.

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REFERENCES

1. Melton LJ, Atkinson EJ, O'Fallon WM, Walmer HW, Riggs BL 1991 Long-term fracture risk prediction with bone mineral measurements made at various skeletal sites. J Bone Miner Res **6:**S1; S136.
2. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA 1994 Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int **4:**277–282.
3. Barrett-Connor E 1995 The economic and human costs of osteoporotic fracture. Am J Med **98**(Suppl 2A)**:**3S–8S.
4. Russell RGG, Croucher PL, Rogers MJ 1999 Bisphosphonates: Pharmacology, mechanisms of action and clinical uses. Osteoporos Int **9**(Suppl 2)**:**S66–S80.
5. Watts NB, Harris ST, Genant HK, Wasnich RD, Miller PD, Jackson RD, Licata AA, Ross P, Woodson GC, Yanover MJ, Mysiw WJ, Kohse L, Rao MB, Steiger P, Richmond B, Chesnut CH III 1990 Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med **323:**73–79.
6. 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 Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet **348:**1535–1541.
7. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH III, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD 1999 Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: A randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA **282:**1344–1352.
8. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Reginster JY, Hip Intervention Program Study group 2001 Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study group. N Engl J Med **344:**333–340.
9. de Groen PC, Lubbe DF, Hirsch LJ, Daifotis A, Stephenson W, Freedholm D, Pryor-Tillotson S, Seleznick MJ, Pinkas H, Wang KK 1996 Esophagitis associated with the use of alendronate. N Engl J Med **335:**1016–1021.
10. Ettinger B, Pressman A, Schein J 1998 Clinic visits and hospital admissions for care of acid-related upper gastrointestinal disorders in women using alendronate for osteoporosis. Am J Manag Care **4:**1377–1382.
11. Papapoulos SE 2001 Bisphosphonates in the management of postmenopausal osteoporosis. In: Marcus R, Feldman D, Kelsey J (eds.) Osteoporosis, 2nd ed. Academic Press, San Diego, CA, USA, pp. 631–649.
12. Gertz BJ, Hollard SD, Kline WF 1993 Clinical pharmacology of alendronate sodium. Osteoporos Int **3**(Suppl 3)**:**13–16.
13. Caro J, Huybrechts K, Ishak K, Naujoks C 2002 The impact of adherence to osteoporosis therapy on fracture rates in actual practice. Value Health **5:**127 (abstract).
14. Kendler DL, Diez-Perez A, Gaines KA, Verbruggen N, Melton ME 2002 Patient preference of once weekly or daily administration of alendronate (Fosamax) for osteoporosis: a randomized crossover study. Osteoporos Int **13**(Suppl 1)**:**S32 (abstract).
15. Palmisano J, Melton M, Lewiecki EM, Rosen R, Bockman RS, Dinh AC, Smith ME, Wang L, Keene W 2002 Preference study of alendronate 70 mg once weekly and alendronate 10 mg once daily in postmenopausal women with osteoporosis. Osteoporos Int **13**(Suppl 1)**:**S36 (abstract).
16. 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.
17. Muhlbauer RC, Bauss F, Schenk R, Janner M, Bosies E, Strein K, Fleisch H 1991 BM21.0955, a potent new bisphosphonate to inhibit bone resorption. J Bone Miner Res **6:**1003–1011.
18. Bauss F, Lalla S, Endele R, Hothorn LA 2002 Effects of treatment with ibandronate on bone mass, architecture, biomechanical properties, and bone concentration of ibandronate in ovariectomized aged rats. J Rheumatol **29:**2200–2208.
19. Monier-Faugere MC, Geng Z, Paschalis EP, Qi Q, Arnala I, Bauss F, Boskey AL, Malluche HH 1999 Intermittent and continuous administration of the bisphosphonate ibandronate in ovariohysterectomized beagle dogs: Effects on bone morphometry and mineral properties. J Bone Miner Res **14:**1768–1778.
20. Smith SY, Recker R, Hannan M, Müller R, Bauss F 2003 Intermittent IV administration of the bisphosphonate ibandronate prevents bone loss and maintains bone strength and quality in ovariectomized cynomolgus monkeys. Bone **32:**45–55.
21. Thiébaud D, Burckhardt P, Kriegbaum H, Huss H, Mulder H, Juttmann JR, Schoter KH 1997 Three monthly IV injections of ibandronate in the treatment of postmenopausal osteoporosis. Am J Med **103:**298–307.
22. Ravn P, Clemmesen B, Riis BJ, Christiansen C 1996 The effect on bone mass and bone markers of different doses of ibandronate: A new bisphosphonate for prevention and treatment of postmenopausal osteoporosis. A 1-year, randomized, double-blind, placebo-controlled, dose-finding study. Bone **19:**527–533.
23. Riis BJ, Ise J, Von Stein T, Bagger Y, Christiansen C 2001 Ibandronate: A comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. J Bone Miner Res **16:** 1871–1878.
24. Schimmer RC, Bauss F 2003 Effect of daily and intermittent use of ibandronate on bone mass and bone turnover in postmenopausal osteoporosis: A review of three phase II studies. Clin Ther **25:**19–34.
25. Ross PD 1995 Morphometric criteria for vertebral fractures based on the individual's vertebral dimensions. In: Genant HK, Jergas M, van Nuijk C (eds.) Vertebral Fracture in Osteoporosis. Radiology Research and Education Foundation, San Francisco, CA, USA, pp. 205–213.
26. Kiel D 1995 Assessing vertebral fractures. National Osteoporosis Foundation Working Group on Vertebral Fractures. J Bone Miner Res **10:**518–523.
27. Genant HK, Engelke K, Fuerst T, Gluer CC, Grampp S, Harris ST, Jergas M, Lang T, Lu Y, Majumdar S, Mathur A, Takada M 1996 Noninvasive assessment of bone mineral and structure: State of the art. J Bone Miner Res **11:**707–730.
28. Bonde M, Qvist P, Fledelius C, Riis BJ, Christiansen C 1994 Immunoassay for quantifying type I collagen degradation products in urine evaluated. Clin Chem **40:**2022–2025.

29. Garnero P, Shih WJ, Gineyts E, Karpf DB, Delmas PD 1994 Comparison of new biochemical markers of bone turnover in late postmenopausal osteoporotic women in response to alendronate treatment. J Clin Endocrinol Metab **79:**1693–1700.
30. Rosenquist C, Qvist P, Bjarnason N, Christiansen C 1995 Measurement of a more stable region of osteocalcin in serum by ELISA with two monoclonal antibodies. Clin Chem **41:**1439–1445.
31. Rosalki SB, Foo AY, Burlina A, Prellwitz W, Stieber P, Neumeier D, Klein G, Poppe WA, Bodenmuller H 1993 Multicenter evaluation of Iso-ALP test kit for measurement of bone alkaline phosphatase activity in serum and plasma. Clin Chem **39:**648–652.
32. 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. FIT Research Group. J Clin Endocrinol Metab **85:**4118–4124.
33. 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.
34. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M 1995 Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate phase III Osteoporosis Treatment study group. N Engl J Med **333:**1437–1443.
35. Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-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. Fosamax International Trial study group. Osteoporos Int **9:**461–468.
36. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R 2000 Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) study group. Osteoporos Int **11:**83–91.
37. Delmas PD, Balena R, Confavreux E 1997 Bisphosphonate risedronate prevents bone loss in women with artificial menopause due to chemotherapy of breast cancer; a double-blind placebo-controlled study. J Clin Oncol **15:**955–962.
38. Passeri M, Baroni MC, Pedrazzoni M, Pioli G, Barbagallo M, Costi D, Biondi M, Girasole G, Arlunno B, Palummeri E 1991 Intermittent treatment with IV 4-amino-1-hydroxybutylidene-1,1-bisphosphonate (AHButBP) in the therapy of postmenopausal osteoporosis. Bone Miner **15:**237–248.
39. Thiébaud D, Burckhardt P, Melchior J, Eckert P, Jacquet AF, Schnyder P, Gobelet C 1994 Two years effectiveness of IV pamidronate (APD) versus oral fluoride for osteoporosis occurring in the menopause. Osteoporos Int **4:**76–83.
40. Filipponi P, Pedetti M, Fedeli L, Cini L, Palumbo R, Boldrini S, Massoni C, Cristallini S 1995 Cyclical clodronate is effective in preventing postmenopausal bone loss: A comparative study with transcutaneous hormone replacement therapy. J Bone Miner Res **10:**697–703.
41. Storm T, Thamsborg G, Steiniche T, Genant HK, Sørenson OH 1990 Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med **322:**1265–1271.
42. Adami S, Felsenberg D, Christiansen C, Robinson J, Lorenc RS, Mahoney P, Coutant K, Schimmer RC, Delmas PD 2004 Efficacy and safety of ibandronate given by IV injection once every 3 months. Bone **34:**881–889.
43. Recker R, Stakkestad JA, Chesnut CH III, Christiansen C, Skag A, Hoiseth A, Ettinger M, Mahoney P, Schimmer RC, Delmas PD 2004 Clinical assessment of IV ibandronate injection once every 3 months in postmenopausal osteoporosis. Bone **34:**890–894.

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