0021-972X/03/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 88(10):4609–4615

doi: 10.1210/jc.2003-022029

Efficacy and Safety of Oral Weekly Ibandronate in the Treatment of Postmenopausal Osteoporosis

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Adherence to oral daily bisphosphonate regimens in postmenopausal osteoporosis is currently suboptimal. Less frequent dosing regimens are likely to improve patient adherence and thus, potentially, patient outcomes. A multicenter, randomized, double-blind, noninferiority study was conducted in 235 women (53–80 yr old; time since menopause ≥ 3 yr) with postmenopausal osteoporosis [lumbar spine (L1–L4) bone mineral density (BMD) T-score ≤ −2] to demonstrate the noninferiority of an oral weekly (20 mg) ibandronate regimen compared with an oral daily (2.5 mg) ibandronate regimen. All patients received daily calcium (500 mg) and vitamin D (400 IU). The primary analysis was the relative change in lumbar spine (L1–L4) BMD from baseline after 48 wk in the per-protocol population. Daily and weekly ibandronate significantly increased spinal BMD by 3.47 and 3.53%, respectively, and provided substantial and similar decreases in biochemical markers of bone turnover. In the primary analysis, noninferiority of the weekly regimen to the daily regimen was demonstrated, with the boundary of the one-sided confidence interval, −0.96%, within both the −1.65% prespecified margin and a more stringent margin of −1.10%. These results demonstrate that oral weekly ibandronate provides the same efficacy and safety as oral daily ibandronate in women with postmenopausal osteoporosis. (*J Clin Endocrinol Metab* 88: 4609–4615, 2003)

ADHERENCE TO ORAL daily bisphosphonate regimens in postmenopausal osteoporosis is currently suboptimal (1, 2). Simplified bisphosphonate dosing regimens may help solve this problem. Given that a strong patient preference for less frequent bisphosphonate dosing schedules has recently been reported (3, 4), less frequent bisphosphonate regimens are likely to improve patient outcomes through their simplicity, leading to improved adherence to therapy. Moreover, less frequent dosing schedules may also provide improved tolerability, with a reduced opportunity for the post-dose upper gastrointestinal (GI) adverse events associated with some bisphosphonates.

Ibandronate, a highly potent, nitrogen-containing bisphosphonate, is the subject of an ongoing oral and iv injection clinical development program (5–10) that aims to exploit the potential of less frequent dosing in postmenopausal osteoporosis. The ability to administer ibandronate in dosing schedules featuring extended between-dose intervals was first demonstrated in animal models. A clinically relevant iv monthly ibandronate regimen (30 μg/kg) was shown to prevent osteopenia in estrogen-depleted cynomolgus monkeys over 16 months (11). Studies of ibandronate in animal models of osteoporosis also suggest that the total administered dose within a given period is an important determinant for efficacy. Ibandronate administered daily (5 of 7 d) or with extended between-dose intervals (on/off wk = 2/11) was shown to have a similar effect on bone volume in ovariohysterectomized dogs (12). In addition, daily and less frequently administered (on/off wk = 1/2, 1/4, or 1/6) ibandronate regimens were shown to provide similar efficacy in preventing bone loss and maintaining bone architecture in aged ovariectomized rats (13).

Recent studies have provided an insight into the clinical validity of less frequent dosing in postmenopausal osteoporosis. Most notably, a recent phase-III fracture study [oral ibandronate osteoporosis vertebral fracture study in North America and Europe (BONE) study] investigating the efficacy and safety of an oral daily ibandronate regimen and oral intermittent ibandronate regimen with an extended between-dose interval of more than 2 months reported substantial and highly significant reductions in vertebral fracture risk in both treatment arms (62% and 50%, respectively), after 3 yr, in women with postmenopausal osteoporosis (8). In addition, the feasibility of a once-weekly dosing concept has been demonstrated in recent studies comparing the efficacy and safety of oral weekly and daily regimens of approximately the same cumulative dose. Schnitzer *et al.* (14) demonstrated the therapeutic equivalence of oral weekly (70 mg) and daily (10 mg) alendronate regimens. Oral weekly (50 mg and 35 mg) and daily (5 mg) risedronate regimens have also been shown to provide similar efficacy and safety (15).

The objective of this study was to demonstrate the noninferiority of an oral weekly ibandronate (20 mg) regimen to the oral daily ibandronate (2.5 mg) regimen investigated in previous studies of ibandronate (5, 7, 8).

Abbreviations: AUC, Area under the curve; BMD, bone mineral density; BONE, oral ibandronate osteoporosis vertebral fracture study in North America and Europe; CI, confidence interval; CTX, C-telopeptide of the α-chain of type I collagen; GI, gastrointestinal; ITT, intent-to-treat; PP, per-protocol.

Subjects and Methods

Participants

It was planned to recruit women who were, at randomization, 55–80 yr old, postmenopausal for at least 3 yr, and had a lumbar spine bone mineral density (BMD) T-score of −2 or less. Women were excluded from participating in the study if they were nonambulatory, had undergone bilateral oophorectomy, or had a disease or disorder known to influence bone metabolism. In accordance with previous studies of ibandronate (5) and risedronate (16), a 6-month 'wash out' period was employed in the current study to minimize the effects of prior therapies known to influence bone metabolism (*e.g.* bisphosphonates). Women were also excluded if they had received fluoride treatment (dose > 10 mg/d) within the last 12 months or for a total duration of more than 2 yr or any investigational drug within the last 30 d. Additional exclusion criteria were renal impairment (serum creatinine > 210 μM), contraindications for calcium therapy, vitamin D deficiency (serum 25-hydroxyvitamin D < 10 ng/ml), and serum calcium concentrations of at least 2.6 or less than 2.0 mM. Ethics review and approval was received from all participating centers. All participants provided written informed consent and were willing and able to comply with the study protocol.

Study design

This was a multicenter, double-blind, randomized, noninferiority study of the efficacy and safety of oral weekly *vs.* oral daily ibandronate in the treatment of postmenopausal osteoporosis. At enrollment, study participants were randomized to receive oral daily (2.5 mg) or weekly (20 mg) ibandronate for 48 wk. Randomization was performed using a predetermined randomization list (based on block randomization), and both patients and investigators were blinded to the treatment assignment. Participants in the weekly ibandronate arm received placebo on the 6 d of the week when no active medication was given. All participants were instructed to take their medication upon rising each morning, with a glass of plain water while in an upright position. Participants were advised not to recline after taking the medication and not to eat or drink (except plain water) for at least 6 h before and at least 30 min after the intake of study medication. All participants received oral daily calcium (500 mg) and vitamin D (400 IU) supplementation. Patients were instructed to take their supplements 1 h before evening meals.

The primary efficacy endpoint was the relative change in lumbar spine (L1–L4) BMD from baseline after 48 wk. Secondary efficacy endpoints were the relative change from baseline in hip BMD (all sites), relative change from baseline, and area under the curve (AUC) for the relative change from baseline in urinary and serum concentrations of the C-telopeptide of the α-chain of type I collagen (urinary CTX/creatinine and serum CTX, respectively) and serum osteocalcin. Measurements of lumbar spine BMD and hip BMD were taken at baseline and at 24 and 48 wk, using dual-energy x-ray absorptiometry (Hologic QDR, Hologic Inc., Bedford, MA; or Lunar DPX, Lunar Corporation, Madison, WI). Within each center, a single dual-energy x-ray absorptiometry machine was used for all measurements. A coefficient of variation of between 0.30–0.73% was observed for all machines, with the majority (86%) within quality control reference values (0.5–0.7%) as defined by Synarc, (Lyon, France). Biochemical markers of bone turnover were measured at baseline and at 12, 24, and 48 wk in all patients and at 1, 2, and 4 wk in a subset of patients (20 patients per treatment group) using Crosslaps (Osteometer, Hawthorne, CA; urinary CTX/creatinine) and Elecsys (Roche Diagnostics, Basel, Switzerland; serum CTX and serum osteocalcin) immunoassays. Safety endpoints included adverse events, laboratory parameters of renal and hepatic function, hematology, and electrolyte balance. All laboratory assessments were performed centrally using standard methodology.

Sample size

Based on the assumption that a clinically significant effect of one half the standardized difference should be excluded in a one-sided 2.5% significance level noninferiority test with a power of 85%, a sample size of 86 evaluable patients per treatment arm was required in a parametric *t* test situation. To account for noncompliant patients (*e.g.* patients excluded from the primary analysis) and a dropout rate of 20%, as well as for efficiency loss caused by nonparametric procedures, it was planned to enroll 220 patients, with 110 patients randomized to each of the two treatment arms.

Analysis populations

All patients enrolled in the study who received at least one dose of study medication and for whom there was at least one follow-up data point recorded were included in the safety analysis. The intent-to-treat (ITT) analysis included all randomized patients in the safety population for whom lumbar spine (L1–L4) BMD was evaluable and measured at baseline and who participated in at least one follow-up visit. The per-protocol (PP) analysis included all patients in the ITT population for whom there were no protocol deviations identified during the blinded review that were deemed to have a significant impact on efficacy, who demonstrated a compliance of at least 75%, who were not excluded because of use of forbidden previous or concomitant medication, and for whom lumbar spine BMD was measured at baseline and for the visit scheduled at wk 48.

Noninferiority analysis

The primary efficacy analysis, the relative change in lumbar spine (L1–L4) BMD after 48 wk, was assessed in a noninferiority comparison of oral daily and weekly ibandronate. For this assessment, the null and alternative hypotheses were defined as: 1) H_o (null hypothesis): there is a relevant difference between the two study treatments, to the advantage of the daily administration of 2.5 mg oral ibandronate, in the relative change in lumbar spine (L1–L4) BMD after 48 wk; and 2) H_1 (alternative hypothesis): there is no relevant difference between the two study treatments as assessed by the limits defined below.

This analysis was based on the PP population because, in a noninferiority study, the imputation of missing values (as in an ITT analysis) might be expected to increase the probability that no difference between the treatment arms would be concluded (type 2 error).

The primary analysis took a parametric approach based on the construction of a one-sided 97.5% confidence interval (CI) of the difference of the means between the two treatment groups (weekly arm minus the daily arm) in the change in lumbar spine BMD. The clinically acceptable margin of noninferiority, given by the boundary of the 97.5% CI of the difference of the means, was prespecified as −1.65%. This margin was calculated as one half of the observed superiority of a daily ibandronate regimen over a placebo regimen (3.30%) in increasing lumbar spine BMD in a similar population (7). Thus, the weekly regimen would not be considered inferior to the daily regimen if the boundary of the one-sided 97.5% CI was at least −1.65%. In accordance with feedback from health authorities on the study design, noninferiority of the weekly regimen to the daily regimen was also tested with a tighter margin of the boundary of the CI (−1.10%) based on one-third of the observed superiority of a daily regimen over a placebo regimen (3.30%; 7). An additional, exploratory analysis of the difference between the two treatment arms was also performed, using the nonparametric 97.5% one-sided CI of the Wilcoxon-Mann-Whitney estimate of stochastic superiority of the weekly regimen over the daily regimen.

The AUC of the relative change in serum osteocalcin and urinary CTX/creatinine was also analyzed using the same procedures as those described for the primary efficacy endpoint. Noninferiority was assumed for the following conditions: 1) AUC of the relative change in serum osteocalcin, if the upper boundary of the CI for the difference was inferior to 10%; 2) AUC of the relative change in urinary CTX/creatinine excretion, if the upper boundary of the CI for the difference was inferior to 23%. As in the analysis of BMD change, margins of noninferiority were calculated as approximately one half of the observed superiority of a daily ibandronate regimen over a placebo regimen (percent) in suppressing the bone markers in a similar population of a previous clinical study (7).

Results

Patient disposition and baseline characteristics

Figure 1 shows the flow of patients through the study. A total of 235 patients were randomized into the study. A total of 121 and 114 women were randomized to the oral daily and

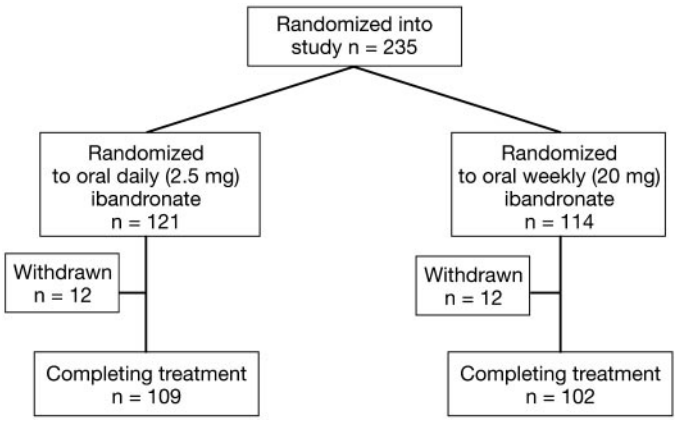

FIG. 1. Patient disposition.

weekly ibandronate treatment arms, respectively. All patients received at least one dose of study medication. A total of 24 patients discontinued treatment prematurely, with 12 patients withdrawing from each of the two study groups. No significant difference between the treatment arms was observed in the time to withdrawal (rank test $P = 0.8981$).

Table 1 provides a summary of the analysis populations and the primary reasons for exclusion. All participants were included in the safety analysis. In total, 15 patients were excluded from the ITT analysis and 32 patients from the PP analysis.

Baseline demographic characteristics were well balanced between the treatment groups. Table 2 shows the baseline demographic, BMD, and biochemical marker of bone turnover characteristics of all patients included in the primary analysis. The treatment groups were well balanced, with respect to BMD and biochemical markers of bone turnover characteristics at baseline. The overall baseline disease and fracture history was similar in both treatment arms.

BMD

Oral daily and weekly ibandronate produced substantial and almost identical increases in lumbar spine (L1–L4) BMD, relative to baseline (Fig. 2). After 48 wk, mean (95% CI) relative increases in lumbar spine BMD of 3.47% (2.68–4.25%) and 3.53% (2.83–4.24%) were observed in the daily and weekly treatment arms, respectively (PP population). The most substantial gains in lumbar spine BMD were detected during the first 24 wk of the study, although BMD continued to increase throughout the entire 48-wk study period. The time course for BMD change was similar for both treatment groups. Similar, significant increases in lumbar spine (L1–L4) BMD were demonstrated in the ITT analysis (Table 3).

In light of the results observed for the primary analysis population (PP), the null hypothesis of superiority of the oral daily ibandronate regimen was rejected by the one-sided 97.5% CI for the difference of the means, with the boundary of −0.96% lying substantially above the predefined limit of −1.65% (Fig. 3). Noninferiority was also confirmed with the more stringent CI limit of −1.10% (Fig. 3). These findings were corroborated by the results of subsequent analyses performed using the nonparametric Wilcoxon-Mann-Whitney estimate of stochastic superiority of the weekly regimen over the daily regimen. Noninferiority of the weekly regimen, compared with the daily regimen, was also demonstrated in the ITT analysis.

TABLE 1. Summary of analysis populations

	Oral daily ibandronate (2.5 mg; n = 121)	Oral weekly ibandronate (20 mg; n = 114)
Safety		
Included	121	114
Excluded	0	0
ITT		
Included	113	107
Excluded	8	7
No observation of lumbar spine [L1–L4] BMD after screening	8	7
Per protocol		
Included	106	97
Excluded	15	17
No observation of lumbar spine [L1–L4] BMD after screening	8	7
No observation of lumbar spine [L1–L4] BMD at visit 7	3	3
Lack of compliance	1	4
Nonpermitted medication	3	2
Poor compliance with dosing instructions	0	1

Substantial and similar increases in BMD were also detected at all hip sites after 48 weeks. Of note, oral daily and weekly ibandronate provided mean (95% CI) relative BMD increases of 2.15% (1.61–2.70%) and 1.74% (1.11–2.37%) at the total hip (Fig. 4A; PP analysis) and 1.62% (0.87–2.36%) and 1.67% (0.88–2.45%) at the femoral neck (Fig. 4B; PP analysis). Exploratory analyses demonstrated no significant differences in the increases in BMD produced by the daily and weekly regimens at all hip sites. The most substantial gains in hip BMD (all sites) were detected during the initial 24-wk period of the study, although BMD continued to increase over the entire study period. Similar, significant increases in proximal femur BMD (all sites) were also noted in the ITT analysis (Table 3), thus corroborating the findings of the PP analysis.

Biochemical markers of bone turnover

Oral daily and weekly ibandronate produced similar and substantial decreases in biochemical markers of bone turnover (Figs. 5–7). After 48 wk, oral daily and weekly ibandronate reduced median serum CTX concentrations by 47% and 44%, respectively; median urinary CTX/creatinine excretions by 54% and 57%, respectively; and median serum osteocalcin concentrations by 34% and 41%, respectively, in the PP population. Similar findings were observed in the ITT analysis (Table 3). As assessed in a subset of patients, suppression of serum CTX, urinary CTX, and serum osteocalcin was observed to occur within the first 4 wk after commencing treatment, with the magnitude of suppression being similar between the daily and weekly treatment groups.

The AUC of the relative changes in markers of bone turnover indicated that the total suppression over the period of

TABLE 2. Baseline patient characteristics (PP population)

	Oral daily ibandronate (2.5 mg; n = 106)	Oral weekly ibandronate (20 mg; n = 97)
Patient characteristics [mean (SD)]		
Age (yr)	66.0 (6.2)	65.5 (6.3)
Time since menopause (yr)	17.7 (7.9)	17.1 (8.2)
Height (cm)	159.8 (6.4)	159.9 (6.1)
Weight (kg)	66.7 (12.9)	67.4 (12.0)
25 (OH) vitamin D at baseline (ng/ml)	32.8 (12.4)	31.4 (11.0)
BMD [mean (SD)]		
Lumbar spine [L1–L4] (g/cm^2)	0.78 (0.08)	0.78 (0.08)
Total hip (g/cm^2)	0.74 (0.11)	0.75 (0.09)
Hip trochanter (g/cm^2)	0.56 (0.09)	0.57 (0.08)
Femoral neck (g/cm^2)	0.64 (0.08)	0.65 (0.08)
Biochemical markers of bone turnover (median[a])		
CTX/creatinine (μg/mmol)	204.31	215.10
Serum CTX (pg/ml)	367.38	343.60
Serum osteocalcin (ng/ml)	30.42	32.56

[a] Because the distribution of biochemical markers of bone turnover was nonnormal, median values were used for all statistical measures.

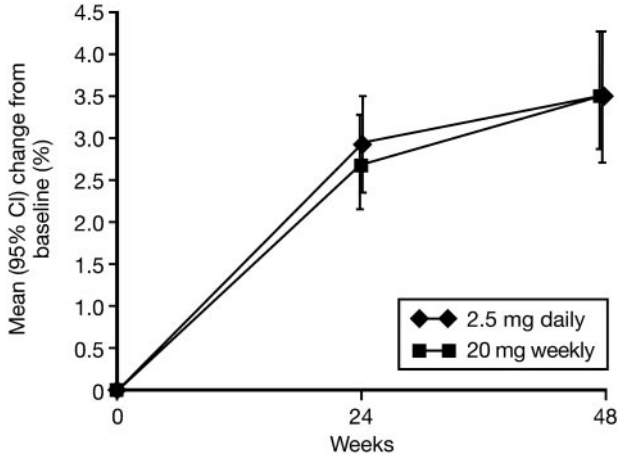

FIG. 2. Time course of mean (95% CI) change in lumbar spine (L1–L4) BMD in the PP population over 48 wk in the oral daily and weekly ibandronate treatment arms.

the study was similar for the two treatment arms, with a marginally greater suppression observed with weekly (compared with daily) treatment. Exploratory tolerance levels for noninferiority of the treatment regimen were prespecified for osteocalcin and urinary CTX/creatinine (<10% and <23%, respectively). The upper boundaries of the CI were below the tolerance margin for both of these markers of bone turnover, demonstrating noninferiority of the weekly regimen, compared with the daily regimen. The noninferiority of the weekly regimen to the daily regimen was further corroborated by the findings of additional analyses performed using the nonparametric Wilcoxon-Mann estimate of stochastic superiority of the weekly regimen *vs.* the daily regimen.

Safety

Oral daily and weekly ibandronate regimens were well tolerated, with a similar incidence of adverse events reported in both treatment arms (Table 4). The most common adverse events reported in the daily and weekly treatment arms were of the GI (33% *vs.* 28%, respectively), musculoskeletal (26% *vs.* 28%, respectively), and general body (23% *vs.* 29%, respectively) systems.

TABLE 3. Relative change (percent) from baseline in lumbar spine and hip BMD and biochemical markers of bone turnover after 48 wk in the ITT analysis

	Oral daily ibandronate (2.5 mg)	Oral weekly ibandronate (20 mg)
BMD [mean (95% CI)]		
n	110	103
Lumbar spine	3.42 (2.64, 4.20)	3.45 (2.75, 4.16)
Total hip	2.09 (1.55, 2.63)	1.81 (1.22, 2.40)
Femoral neck	1.63 (0.91, 2.34)	1.65 (0.92, 2.38)
Trochanter	2.72 (1.90, 3.53)	2.24 (1.46, 3.02)
Wards triangle	4.71 (3.05, 6.38)	4.34 (2.91, 5.77)
Biochemical markers of bone turnover (median[a])		
n	108	103
Serum CTX	−43.4	−42.6
Serum osteocalcin	−34.3	−39.4
CTX/creatinine	−52.2	−55.0

[a] Because the distribution of biochemical markers of bone turnover was nonnormal, median values were used for all statistical measures.

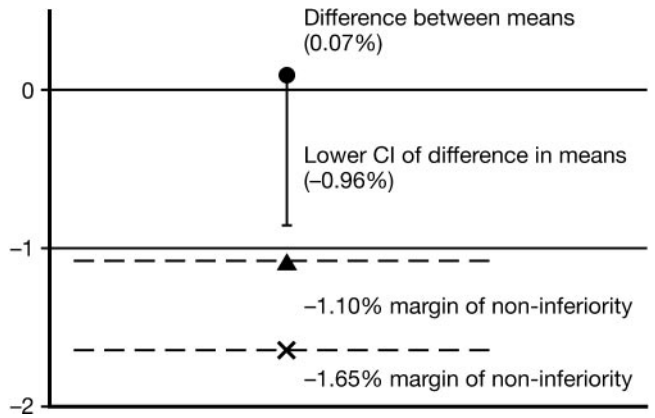

FIG. 3. Graphical representation of the noninferiority of the oral weekly ibandronate regimen, compared with the oral daily ibandronate regimen.

The incidence of adverse events considered possibly related to the study medication was also similar in the daily and weekly treatment arms (Table 4).

Weekly ibandronate demonstrated a further improved GI

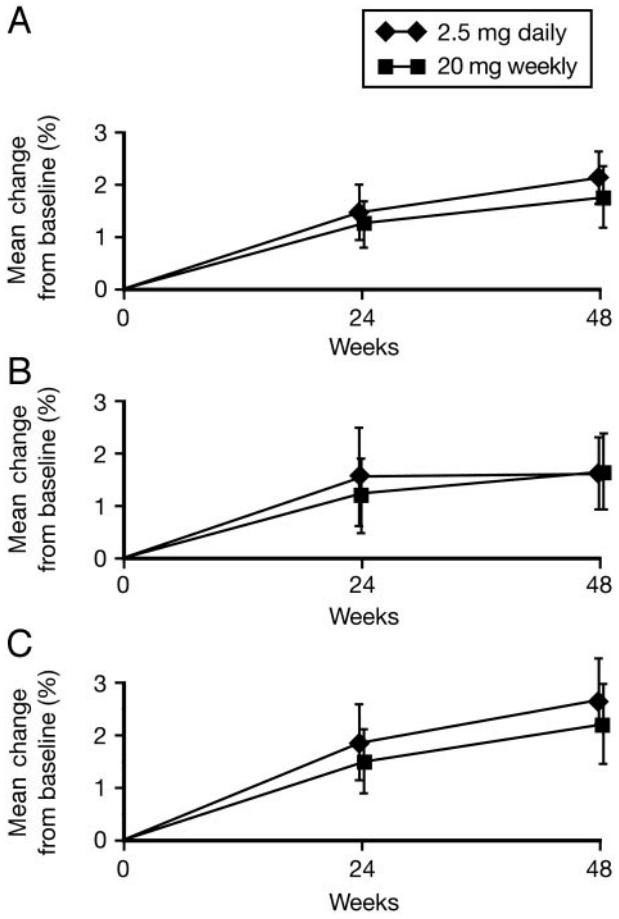

FIG. 4. Time course of mean (95% CI) change in BMD at the total hip (A), femoral neck (B), and hip trochanter (C) in the PP population, over 48 wk in the oral daily and weekly ibandronate treatment arms.

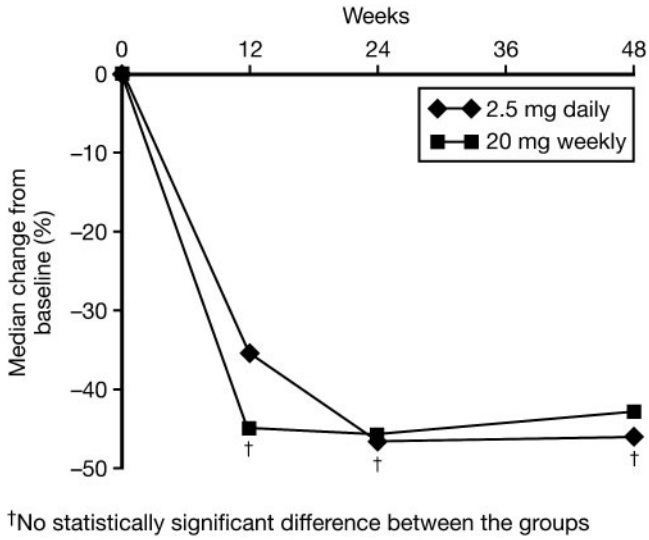

FIG. 5. Time course of median change in serum CTX concentrations in the PP population, over 48 wk in the oral daily and weekly ibandronate treatment arms.

safety, compared with daily ibandronate. Overall, the number of adverse events reported for the digestive system was 25% lower in those patients treated with weekly ibandronate

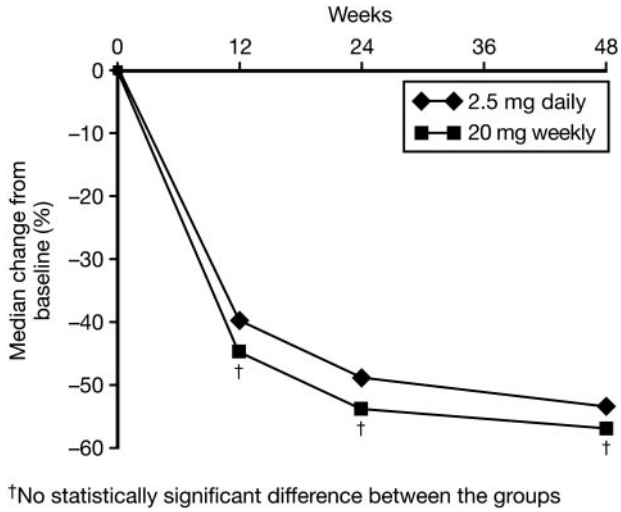

FIG. 6. Time course of median change in urinary CTX/creatinine concentrations in the PP population, over 48 wk in the oral daily and weekly ibandronate treatment arms.

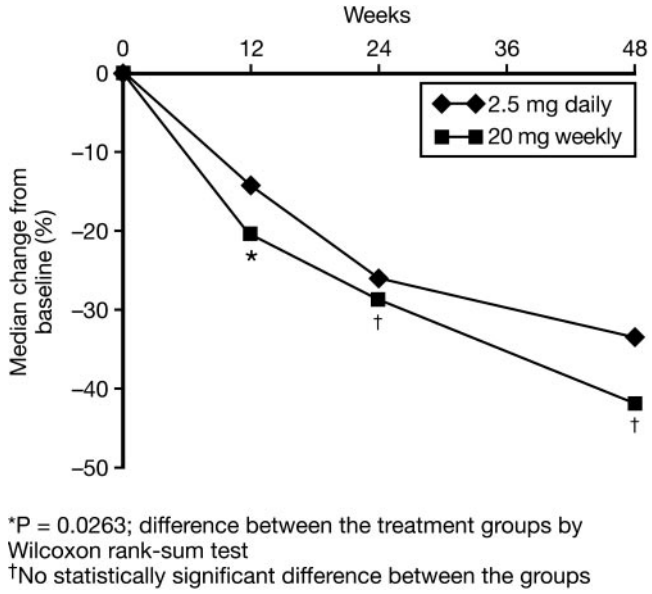

FIG. 7. Time course of median change in serum osteocalcin concentrations in the PP population, over 48 wk in the oral daily and weekly ibandronate treatment arms.

(n = 27), compared with the daily group (n = 36; $P = 0.294$). Also, the incidence of digestive system adverse events considered possibly related to the study medication was lower in the weekly treatment arm than in the daily treatment arm (16% *vs.* 22%, respectively), with dyspepsia and constipation being the most commonly reported treatment-related adverse events in the daily (9% and 6%, respectively) and weekly (6% and 4%, respectively) treatment arms.

A total of 10 patients withdrew prematurely from each treatment arm because of an adverse event, the most common of which being dyspepsia (three patients in the daily treatment arm, one patient in the weekly treatment arm). Additional adverse events that led to the withdrawal of more than 1 patient were: vomiting (2), depression (2), and GI pain (3). Of the 20 patients withdrawing from treatment because

TABLE 4. Summary of adverse events (AE; safety population)

	Oral daily ibandronate (2.5 mg; n = 121)	Oral weekly ibandronate (20 mg; n = 114)
Any AEs	99 (82%)	89 (78%)
Drug-related AEs	38 (31%)	39 (34%)
Serious AEs	12 (10%)	9 (8%)
Drug-related serious AEs	0	0
AEs leading to withdrawal	10 (8%)	10 (9%)
Drug-related AEs leading to withdrawal	5 (4%)	6 (5%)
Serious AEs leading to withdrawal	4 (3%)	2 (2%)
Drug-related serious AEs leading to withdrawal	0	0
Death	0	0

of an adverse event, 11 of these patients (55%) did so because of an adverse event considered possibly related to the study treatment. A treatment-related adverse event led to the withdrawal of five patients from the daily treatment arm and six patients from the weekly treatment arm.

A total of 12 (10%) patients in the daily treatment arm and nine (8%) patients in the weekly treatment arm experienced a serious adverse event. Serious adverse events led to the withdrawal of four patients from the daily treatment arm and two patients from the weekly treatment arm. None of the serious adverse events reported were considered possibly related to study treatment.

Discussion

The present study compared the efficacy and safety of an oral once-weekly (20 mg) ibandronate regimen with an oral daily (2.5 mg) ibandronate regimen in 235 women with postmenopausal osteoporosis. After 48 wk, significant and almost-identical increases in lumbar spine (L1–L4) BMD were seen in the daily and weekly treatment arms (3.47% and 3.53%, respectively). Similar and significant increases in hip BMD (all sites) and decreases in biochemical markers of bone turnover were also observed. In the primary efficacy analysis of the relative change in lumbar spine (L1–L4) BMD from baseline after 48 wk, noninferiority of the weekly regimen (compared with the daily regimen) was demonstrated, with the boundary of the one-sided CI, −0.96, within both the −1.65% prespecified margin and a more stringent margin of −1.10%. These findings were supported by secondary and exploratory analyses of BMD at other sites and in biochemical markers of bone turnover. These data demonstrate that oral weekly and daily ibandronate regimens provide the same efficacy in treating women with postmenopausal osteoporosis. These results are also consistent with those of Schnitzer *et al.* and Brown *et al.* (14, 15), who demonstrated the therapeutic equivalence of oral weekly and daily alendronate and risedronate regimens of the same cumulative weekly dose in the treatment of patients with postmenopausal osteoporosis.

The mean relative increases in lumbar spine and hip BMD observed in the daily ibandronate treatment arm were slightly lower than those observed at a similar time point (1 yr) in the BONE study, in which a substantial antifracture effect was reported (8). Because the ingestion of food and other beverages is known to influence the oral bioavailability of bisphosphonates, the smaller BMD gains observed in the current study (compared with the BONE study) are likely explained by the 'at least 30-min' post-dose fast stipulation employed, compared with the 'at least 60-min' stipulation used in the BONE study. Notably, data from a separate clinical trial investigating the effects of changes in post-dose fasting periods on the bioavailability of ibandronate indicate an approximately 30% reduction in bioavailability when the fasting period is reduced from 60 min to 30 min (17). Although the reduced post-dose fasting period could be viewed as a bias toward noninferiority, it is difficult to see how this would have eliminated a true difference between the regimens, should this have existed. However, there may be a slight reservation as to whether the same findings would be demonstrated with an 'at least 60-min' post-dose fast stipulation.

The reduction in oral bioavailability associated with the 'at least 30-min' post-dose fast stipulation may also provide an explanation for the relatively slow, although clinically significant, decline in CTX/creatinine, serum CTX, and serum osteocalcin concentrations observed in the current study and, in the case of serum osteocalcin, the failure to attain a clear nadir over the 48-wk study period. Despite this observation, it is worthwhile to note that no significant differences were observed between the treatment arms for both the relative change and the AUC of the relative change of the studied biochemical markers of bone turnover at the 24- and 48-wk assessment points.

Oral daily and weekly ibandronate regimens were well tolerated, with a similar incidence of adverse events reported in both treatment arms. No difference was observed between the treatment arms in the distribution of adverse events, serious adverse events, treatment-related adverse events, or withdrawals because of adverse events. However, weekly ibandronate showed improved GI safety over daily ibandronate, with a lower incidence of GI adverse events in the weekly than the daily treatment group.

The simplicity and improved patient convenience associated with less frequent bisphosphonate regimens, such as once-weekly schedule, may have a positive impact on therapeutic outcomes as a consequence of improved adherence to therapy. Patient convenience may be further improved by the development of administration schedules that feature extended between-dose intervals, beyond the weekly dosing concept. Ongoing studies of ibandronate aim to evaluate new dosing paradigms, including a once-monthly dosing option, which are predicted to further enhance patient convenience in postmenopausal osteoporosis.

Conclusions

This study demonstrates that an oral weekly ibandronate regimen is as efficacious and well tolerated as an oral daily ibandronate regimen in the treatment of postmenopausal osteoporosis. Despite the higher single dose, GI safety was improved with the weekly regimen, as indicated by the lower incidence of GI adverse events. These findings may have important implications for the future optimization of dosing regimes with extended between-dose intervals, which are predicted to improve efficacy through simple and convenient dosing schedules that ensure greater patient compliance, relative to current treatment options.

Acknowledgments

We thank Erik Eriksen, Ole Sorensen, David Doyle, Ranuccio Nuti, Sergio Ortolani, Majed Khraishi, Hans-Joerg Haeuselmann, Rene Rizzoli, Gerd Finkenstedt, Lorrie Dixon, Juergen Ise, Vincenzo Garzia, and Giuseppe Girasole for their significant contribution to the study.

Received January 2, 2003. Accepted June 24, 2003.

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This study was sponsored by F. Hoffmann-La Roche Ltd., Basel, Switzerland.

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