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Monthly Oral Ibandronate Therapy in Postmenopausal Osteoporosis: 1-Year Results From the MOBILE Study

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ABSTRACT: Once-monthly (50/50, 100, and 150 mg) and daily (2.5 mg; 3-year vertebral fracture risk reduction: 52%) oral ibandronate regimens were compared in 1609 women with postmenopausal osteoporosis. At least equivalent efficacy and similar safety and tolerability were shown after 1 year.

Introduction: Suboptimal adherence to daily and weekly oral bisphosphonates can potentially compromise therapeutic outcomes in postmenopausal osteoporosis. Although yet to be prospectively shown in osteoporosis, evidence from randomized clinical trials in several other chronic conditions shows that reducing dosing frequency enhances therapeutic adherence. Ibandronate is a new and potent bisphosphonate with antifracture efficacy proven for daily administration and also intermittent administration with a dose-free interval of >2 months. This report presents comparative data on the efficacy and safety of monthly and daily oral ibandronate regimens.
Materials and Methods: MOBILE is a 2-year, randomized, double-blind, phase III, noninferiority trial. A total of 1609 women with postmenopausal osteoporosis were assigned to one of four oral ibandronate regimens: 2.5 mg daily, 50 mg/50 mg monthly (single doses, consecutive days), 100 mg monthly, or 150 mg monthly.
Results: After 1 year, lumbar spine BMD increased by 3.9%, 4.3%, 4.1%, and 4.9% in the 2.5, 50 /50, 100, and 150 mg arms, respectively. All monthly regimens were proven noninferior, and the 150 mg regimen superior, to the daily regimen. All monthly regimens produced similar hip BMD gains, which were larger than those with the daily regimen. All regimens similarly decreased serum levels of C-telopeptide, a biochemical marker of bone resorption. Compared with the daily regimen, a significantly larger proportion of women receiving the 100 and 150 mg monthly regimens achieved predefined threshold levels for percent change from baseline in lumbar spine (6%) or total hip BMD (3%). All regimens were similarly well tolerated.
Conclusions: Monthly ibandronate is at least as effective and well tolerated as the currently approved daily ibandronate regimen in postmenopausal osteoporosis.
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Key words: osteoporosis, bisphosphonate, ibandronate, noninferiority, monthly

INTRODUCTION

Osteoporosis is a common chronic condition leading to a high risk of fragility fractures, which imposes a considerable and growing socioeconomic burden.[1–3] It is estimated that one in three women will have an osteoporosis-related fracture during their lifetime,[4] resulting in increased disability[5,6] and mortality,[7,8] with direct financial expenditures of between $10 and $15 billion annually in the United States.[9]

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Because of their proven antifracture efficacy and good tolerability, oral nitrogen-containing bisphosphonates have become the mainstay of treatment for postmenopausal osteoporosis.[10–14] Long-term treatment is required for optimal and sustained therapeutic benefits.[15–17] A growing body of evidence suggests that adherence with current osteoporosis medications, including daily and weekly oral bisphosphonates, is suboptimal[18–24] and can compromise therapeutic outcomes.[21,22,24] Evidence from randomized clinical studies in several other chronic conditions shows that reducing dosing frequency improves therapeutic adherence,[25–27] although this is yet to be prospectively shown in osteoporosis.

Ibandronate is a potent, nitrogen-containing bisphosphonate.[28] Potency, combined with favorable tolerability[10] and bone-binding characteristics,[29] allow ibandronate to be effectively administered less frequently than weekly. Recent findings show that oral ibandronate, whether given daily (2.5 mg) or intermittently (dosing free interval > 2 months), significantly reduces 3-year vertebral fracture risk by 52% and 50%, respectively, and is well tolerated in postmenopausal osteoporosis.[10] A subsequent pilot study showed the feasibility of once-monthly oral ibandronate dosing.[30]

MOBILE (Monthly Oral iBandronate In LadiEs) is a 2-year, multinational, phase III, noninferiority study designed to compare the efficacy and safety of monthly oral ibandronate regimens with the efficacious daily oral ibandronate regimen. Herein, we review the 1-year efficacy and safety findings from this study.

MATERIALS AND METHODS

Study participants

All participants were ambulatory postmenopausal women (55–80 years of age; at least 5 years since menopause) with osteoporosis (mean lumbar spine [L_2–L_4] BMD T score < –2.5 and ≥ –5.0, as derived from manufacturer-specific reference databases for DXA on GE Lunar [Madison, WI, USA] and Hologic [Bedford, MA, USA] instruments). Eligible patients also included those with controlled dyspeptic symptoms, history of nonrecurring peptic ulcers, and/or taking medications with potential for gastrointestinal (GI) irritation. Patients with uncontrolled active or recurrent peptic ulcer disease were excluded. Additional exclusion criteria were a disease, disorder, or therapy (within the last 6 months) known to influence bone metabolism; prior treatment with oral or intravenous bisphosphonates; fluoride treatment within the last 12 months or for a total duration of >2 years; renal impairment (serum creatinine > 2.4 mg/dl, equivalent to 216 μM); and contraindications to calcium or vitamin D therapy. Baseline radiographic assessment for prevalent vertebral fractures was not performed in this study. The Institutional Review Boards of the participating centers approved the study. All participants provided written informed consent.

Study design

MOBILE is a 2-year, randomized, double-blind, parallel-group, phase III, noninferiority study, involving 65 centers in the United States, Canada, Europe, Australia, South Africa, Mexico, and Brazil.

Study medication

Eligible participants were randomized to receive one of four ibandronate regimens for 2 years: 2.5 mg daily, 50 mg/50 mg monthly (single doses on consecutive days), 100 mg monthly, or 150 mg monthly. Participants also received daily or monthly oral placebo medication to maintain blinding. Study medication was taken after an overnight fast of at least 6 h and with 240 ml of plain water. Participants were instructed to maintain an upright posture and continue fasting for at least 60 minutes after dosing. Daily oral calcium (500 mg) and vitamin D (400 IU) was provided.

Study endpoints

Primary efficacy endpoint: The primary efficacy endpoint was percent change from baseline in mean lumbar spine (L_2–L_4) BMD after 1 year, as measured by DXA.

Secondary efficacy endpoints: Percent change from baseline in mean proximal femur (total hip, trochanter, and femoral neck) BMD was also assessed after 1 year.

A prespecified BMD responder analysis examined the proportion of patients in each study arm achieving increases in lumbar spine and/or total hip BMD above baseline after 1 year. The proportion of patients achieving defined increases in lumbar spine or total hip BMD that have previously been associated with vertebral[31] and nonvertebral[32] antifracture efficacy was also prospectively evaluated (≥6% and ≥3%, respectively).

Serum levels of C-telopeptide (sCTX) were measured at baseline and after 3, 6, and 12 months. Blood samples for sCTX assessments were taken at the end of the dosing interval (at least 3 weeks after dosing), after an overnight fast of at least 6 h, between 8:00 a.m. and 10:00 a.m., and were processed at a central laboratory (Synarc, Lyon, France).

Safety parameters

Adverse events were continuously monitored, with upper GI adverse events being of special interest. Laboratory safety parameters were also assessed in blood samples taken at screening and after 6 and 12 months. Samples were processed through a central laboratory (MDS, Les Ponts de Baillet, France). Clinical vertebral and nonvertebral fractures were recorded as adverse events.

Randomization

To ensure comparable distribution of baseline BMD across treatment arms, eligible patients were stratified before randomization by center and baseline lumbar spine (L_2–L_4) BMD T score: < –2.5 and ≥ –3.0; < –3.0 and ≥ –3.5; < –3.5 and ≥ –5.0. A centralized telephone "call in" system was used to randomize patients to treatment using adaptive minimization (Interactive Voice Response System, ClinPhone Ltd., Nottingham, UK).

Statistical analysis

Analysis populations: Compared with per protocol analysis, intent-to-treat (ITT) analysis is generally associated with higher variability and a reduced treatment effect because of inclusion of "nonconforming" patients. Consequently, in MOBILE, the per protocol population was the primary analysis population for all efficacy variables, because it is considered the most conservative approach to detecting actual differences among treatments in the noninferiority analysis.[33] Participants ($n = 319$) were excluded from the per protocol population if they had received no dose of study medication ($n = 7$); a baseline lumbar spine (L_2–L_4) BMD T score > –2.5 ($n = 15$); poor adherence (defined as taking <75% of study medication) with the daily or monthly medication schedule ($n = 269$); unconfirmed menopausal status ($n = 1$); forbidden concomitant disease ($n = 4$); forbidden treatment before study ($n = 34$); lack of efficacy follow-up information ($n = 30$); or lack of reliable BMD data ($n = 96$).

To confirm the robustness of findings, ITT analyses were also performed for all efficacy endpoints. Participants ($n = 37$) were excluded from the ITT analysis if they had no efficacy follow-up information ($n = 36$) or received no dose of study medication ($n = 7$).

The safety population comprised all participants who received at least one dose of study medication, including those withdrawn prematurely, and had at least one follow-up data point. Participants ($n = 26$) were excluded from the safety analysis if no study medication was received ($n = 7$) or no safety follow-up information was available ($n = 19$).

Noninferiority analysis of the primary efficacy variable: To establish efficacy, the percent change from baseline in lumbar spine BMD provided by the monthly regimens was compared with that provided by the daily regimen using a noninferiority analysis.[33] This analysis was also used for the demonstration of therapeutic equivalence for weekly and daily oral risedronate.[34] From previous studies, the minimum difference between placebo and the daily regimen for a significant percent change from baseline in lumbar spine BMD after 1 year was estimated to be 3.3%.[35,36] In MOBILE, the tolerance margin for noninferiority was set at 30% of this difference, which equates to a 1% change in spinal BMD. Noninferiority would be concluded if the lower boundary of the one-sided 97.5% CI for the difference in the means between the monthly and daily regimens was $\geq -1\%$.

Superiority analysis for the primary efficacy variable: If noninferiority was shown, superiority of the monthly regimens to the daily regimen would be tested, using ANOVA of the percent change from baseline in lumbar spine BMD after 1 year.

Analysis of secondary efficacy variables: The methods used for analyzing BMD at other skeletal sites and sCTX were the same as those used for the primary efficacy variable. Percentage responders were compared using χ^2 tests.

Analysis of safety variables: The safety analysis included all adverse events reported during the first year of the study, the frequency and incidence of which were calculated on a per patient basis.

Sample size calculation: For the primary variable, the underlying hypothesis was that the monthly and daily regimens provide similar efficacy. Using a margin of clinical equivalence of $\geq -1\%$, an assumed SD of 4.5%, a one-sided 2.5% significance level noninferiority test, and a power of 80%, a sample size of 318 evaluable patients per treatment arm would be needed for a parametric *t*-test. To account for nonadherent patients and a projected drop-out rate of 20%, a minimum of 1592 patients would be required.

RESULTS

Patient disposition and baseline characteristics

A total of 2410 patients were screened. Of these, 1609 were randomly assigned to one of the four treatment arms, and 1366 completed 1 year of treatment (Fig. 1). Sixty (15%) patients in the daily arm, 49 (12%) in the 50/50 mg arm, 56 (14%) in the 100 mg arm, and 52 (13%) in the 150 mg arm prematurely withdrew from treatment (safety population). Baseline patient characteristics were well balanced across the treatment groups (safety population; Table 1).

Efficacy analysis

Lumbar spine BMD: After 1 year, similar increases in lumbar spine BMD were observed in all treatment arms: 4.3%, 4.1%, and 4.9% in the 50/50, 100, and 150 mg monthly groups, respectively, compared with 3.9% in the 2.5 mg daily group (Fig. 2). The 97.5% CIs for the between-group differences (i.e., monthly regimen minus daily regimen) in percent change in lumbar spine BMD were –0.09, 1.12 (50/50 mg); –0.42, 0.81 (100 mg); and 0.38, 1.60 (150 mg). For each comparison, the lower boundary of the one-sided 97.5% CI was above the prespecified margin of noninferiority (–1%; Fig. 3). As such, all monthly regimens were noninferior to the daily regimen. Subsequent, prospective statistical analyses showed the superiority of the 150 mg monthly regimen to the 2.5 mg daily regimen ($p = 0.002$). Comparable findings were reported in the ITT population: 4.2%, 3.9%, and 4.8% in the 50/50, 100, and 150 mg monthly groups, respectively, compared with 3.7% in the 2.5 mg daily group (noninferior versus daily for all monthly groups; $p < 0.0001$ versus daily for the 150 mg monthly group).

Hip BMD: As observed for the lumbar spine, similar increases in hip BMD (total hip, trochanter, and femoral neck) were shown after 1 year (Fig. 2). Comparable findings were observed for the ITT population.

Responder analysis of lumbar spine and total hip BMD: After 1 year, the majority of patients achieved increases in lumbar spine or total hip BMD above baseline (Fig. 4). Compared with the daily arm, significantly more patients in the 150 mg monthly arm achieved increases in lumbar spine BMD above baseline and significantly more patients in the 100 and 150 mg monthly arms attained gains in total hip BMD. Likewise, significantly more patients in the 100 and 150 mg monthly arms achieved substantial increases in lumbar spine BMD (>6%) and total hip

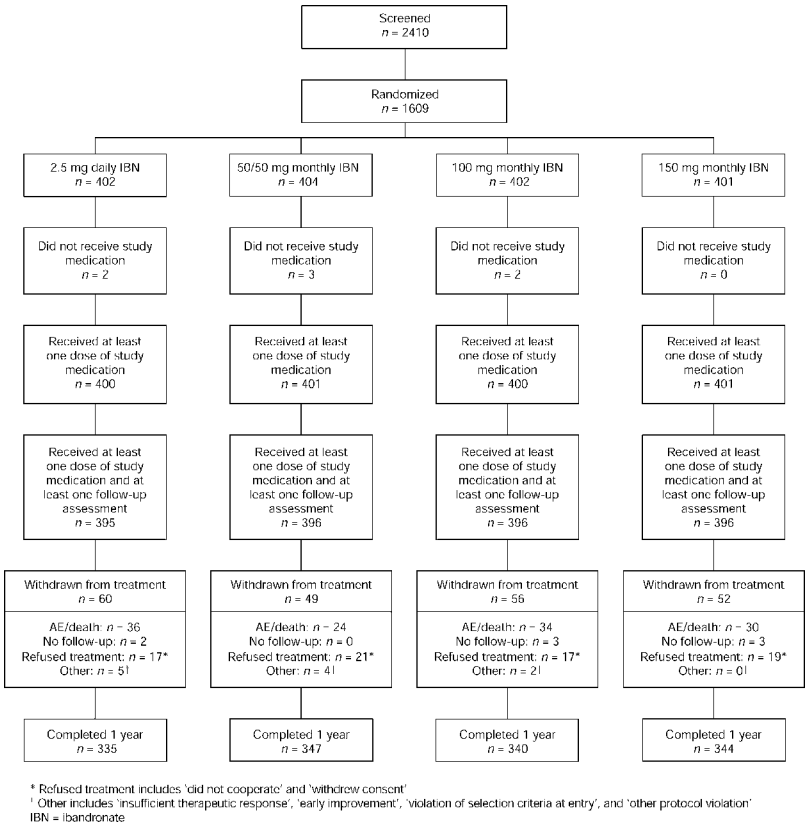


FIG. 1. Patient disposition.

TABLE 1. DEMOGRAPHICS (SAFETY POPULATION)

	Dose			
	2.5 mg (n = 395)	*50/50 mg (n = 396)*	*100 mg (n = 396)*	*150 mg (n = 396)*
Age (years)*	65.8	66.0	66.2	66.2
Weight (kg)*	64.1	64.1	64.0	63.7
Height (cm)*	157.1	157.4	157.3	157.9
Body mass index (kg/m^2)*	25.9	25.8	25.9	25.5
Years since menopause*	18.3	18.7	19.1	18.3
History of previous fractures (%)	192 (48.9)	183 (46.3)	180 (45.5)	185 (46.7)
Lumbar spine (L_2–L_4) BMD (g/cm^2)*	0.755	0.756	0.756	0.754
Lumbar spine (L_2–L_4 BMD (T score)*	–3.3	–3.3	–3.3	–3.3
sCTX (median, ng/ml)†	0.49	0.52	0.51	0.50
25-OH-D (ng/ml)*	25.7	24.4	25.1	24.7

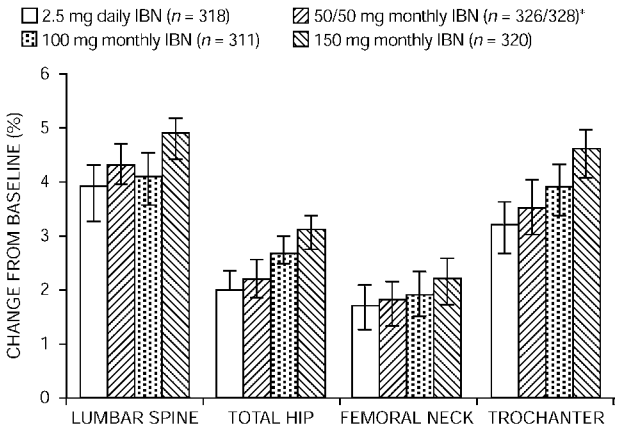
* Mean values.
† Median values.

BMD (>3%), relative to the daily arm. In addition, more patients in the 100 and 150 mg monthly arms achieved gains in both lumbar spine and total hip BMD above baseline versus the daily arm ($p \leq 0.001$ for 100 and 150 mg versus 2.5 mg).

Serum CTX: After 3 months, similar decreases in sCTX were observed in all treatment arms, which were maintained throughout the study period (Fig. 5). After 1 year, median sCTX levels were decreased by 62.8%, 66.7%, and 75.8% in the 50/50, 100, and 150 mg monthly arms, respectively, compared with 67.3% in the daily arm. Comparable findings were obtained in the ITT analysis.

Safety analysis

The incidence of drug-related and/or unrelated adverse events was comparable across the treatment arms (Table 2). A slightly higher overall incidence of serious adverse events was observed in the monthly arms versus the daily arm, which was caused by sporadic events in body systems that had a low frequency of events. For the most commonly represented body systems (GI disorders, cardiac disorders, infections, and infestations), the incidence was similar across treatment arms. Almost all serious adverse events were considered unrelated to study medication, with the six



* n = 328 for lumbar spine BMD and n = 326 for proximal femur BMD
IBN = ibandronate

FIG. 2. Mean (95% CI) percent change from baseline in lumbar spine and proximal femur (total hip, femoral neck, trochanter) BMD after 1 year (per protocol population).

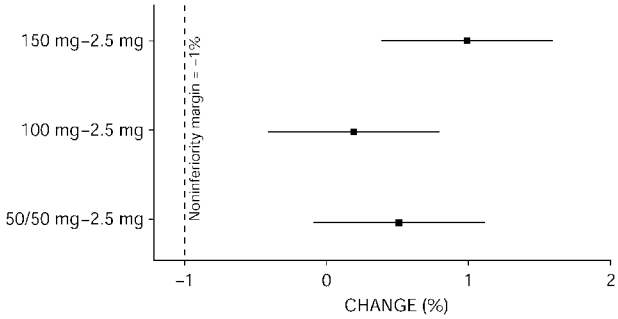
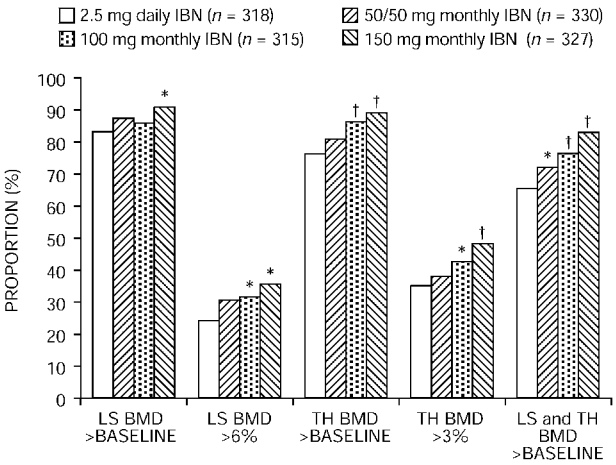


FIG. 3. Forest plot of the difference in the means (95% CI) of the mean percent change from baseline in lumbar spine (L_2–L_4) BMD between the monthly and daily oral ibandronate regimens after 1 year (per protocol population).



* $p < 0.05$ vs 2.5 mg daily IBN
† $p \leq 0.001$ vs 2.5 mg daily IBN

LS = lumbar spine
TH = total hip

FIG. 4. Proportion of participants considered responders to daily or monthly oral ibandronate (per protocol population).

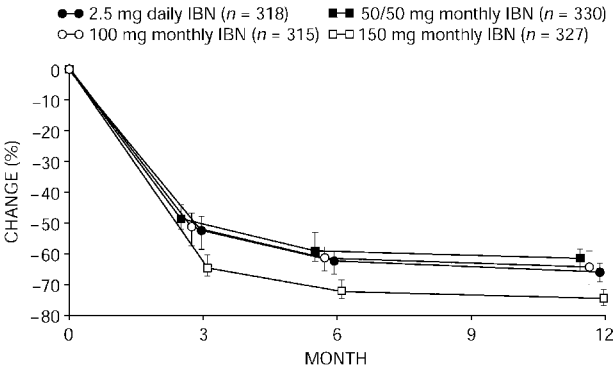


FIG. 5. Time-course of median (95% CI) percent change from baseline in levels of sCTX (per protocol population).

serious adverse events considered related to treatment evenly distributed among the treatment groups.

The incidence of upper GI adverse events was comparable across the treatment arms, as was the incidence of nausea, the most frequently reported symptom. As expected, the incidence of upper GI events was increased in patients with prior history of upper GI disorder versus those without. However, the incidence of upper GI adverse events was similar in the daily, 50/50 mg, and 100 mg groups and lower in the 150 mg group (Table 2). Likewise, although the overall incidence of upper GI events was increased in patients receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), the incidence of upper GI events was well balanced across the monthly and daily arms (Table 2).

In the monthly arms, the number of patients reporting any of a group of 33 influenza-like symptoms (e.g., myalgia, nausea, pyrexia) within 3 days of the monthly intake was slightly higher compared with the daily regimen: 26 (6.6%), 27 (6.8%), and 33 (8.3%) events were observed in the 50/50, 100, and 150 mg monthly arms, respectively, compared with 11 (2.8%) events in the daily arm. The incidence of diagnosed influenza-like illness was low (0.3–3.0%) and consistent with previous observations with ibandronate and other orally administered nitrogen-containing bisphosphonates.[37,38] Most events were mild to moderate in intensity, occurred with the initial administration, were generally of short duration, resolved without symptomatic treatment, and did not result in increased withdrawals.

Clinical fractures identified as adverse events showed no statistically significant differences between the treatment arms after 1 year.

DISCUSSION

The MOBILE study was initiated to compare the efficacy and safety of various monthly ibandronate dose regimens with the daily ibandronate regimen of proven antifracture efficacy.[10] Similar comparative trials have been used for the demonstration of therapeutic equivalence of weekly versus daily oral bisphosphonates, using BMD rather than

Table 2. Overall Summary of Safety (Safety)

	Dose			
	2.5 mg (n = 395)	*50/50 mg (n = 396)*	*100 mg (n = 396)*	*150 mg (n = 396)*
Overall				
Any adverse event	273 (69.1)	264 (66.7)	268 (67.7)	277 (69.9)
Any drug-related adverse event	119 (30.1)	106 (26.8)	130 (32.8)	129 (32.6)
Any drug-related adverse event leading to withdrawal	29 (7.3)	20 (5.1)	25 (6.3)	23 (5.8)
Any serious adverse event	19 (4.8)	27 (6.8)	31 (7.8)	28 (7.1)
Any drug-related serious adverse event	2 (0.5)	2 (0.5)	2 (0.5)	0 (0)
Any drug-related serious adverse event leading to withdrawal	1 (0.3)	1 (0.3)	0 (0)	0 (0)
Adverse events of special interest				
Upper GI adverse events	71 (18.0)	63 (15.9)	86 (21.7)	67 (16.9)
Upper GI adverse events in patients with prior history of upper GI disorder	16/42 (38.1)	17/46 (37.0)	22/48 (45.8)	10/51 (19.6)
Upper GI adverse events in patients receiving concomitant NSAIDs	33/179 (18.4)	39/193 (20.2)	46/181 (25.4)	34/186 (18.3)
Influenza-like symptoms*	11 (2.8)	26 (6.6)	27 (6.8)	33 (8.3)

Values are *n* (%).
* Occurring within 72 h of dosing and lasting for no longer than 7 days.

antifracture endpoints.[34,39,40] The 1-year results from MOBILE show that monthly ibandronate produces increases in lumbar spine BMD that are at least comparable with or even superior to those observed with daily ibandronate. For the tested monthly regimens (50/50, 100, and 150 mg), the criterion for noninferiority versus the daily regimen was fulfilled. Furthermore, superiority of the 150 mg monthly regimen to the daily regimen was prospectively shown. In addition to spinal BMD, the monthly and daily regimens produced similar and significant increases in hip BMD (total hip, femoral neck, and trochanter). Therefore, in women with postmenopausal osteoporosis, monthly ibandronate is at least as effective for BMD endpoints as daily ibandronate.

These results are supported by the findings from the prespecified responder analyses. These analyses show that a significantly larger proportion of women receiving 100 and 150 mg monthly ibandronate achieve increases in lumbar spine and/or total hip BMD of a defined magnitude after 1 year compared with daily ibandronate.

In tandem with these BMD gains, monthly and daily ibandronate provided similar decreases in sCTX after 1 year.

Monthly ibandronate was well tolerated, with a safety profile similar to daily ibandronate. Importantly, the incidence of treatment-related and/or unrelated adverse events, including upper GI adverse events, was generally comparable across treatment arms, despite the higher single doses in the monthly arms. Whereas the 150 mg arm showed a comparatively low incidence of upper GI events in patients with prior history of upper GI disorder, a similar incidence of upper GI events was seen with the monthly and daily regimens in patients with prior history of upper GI disorder or receiving concomitant NSAIDs. These findings are consistent with the previously reported safety and tolerability profile of oral ibandronate in postmenopausal osteoporosis.[10]

In addition to efficacy and safety, the need for therapeutic adherence should also be considered when identifying the most appropriate treatment for an individual patient. With bisphosphonates, long-term therapeutic adherence is required for optimal and sustained therapeutic benefit.[15–17] However, recent reports suggest that adherence with current osteoporosis medications is suboptimal[18–24] and can negatively impact therapeutic outcomes.[21,22,24] Evidence from a range of therapeutic areas, including osteoporosis, shows that less frequent regimens enhance therapeutic adherence.[25–27] The impact of less frequent dosing with monthly oral ibandronate on therapeutic adherence is being studied.

In summary, once-monthly oral ibandronate is at least as effective and well tolerated as a conventional daily oral ibandronate regimen in postmenopausal osteoporosis.

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