

Efficacy and Tolerability of Intravenous Ibandronate Injections in Postmenopausal Osteoporosis: 2-Year Results from the DIVA Study

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ABSTRACT. Objective. An effective and well tolerated intravenous (IV) bisphosphonate could provide a new treatment method for patients with osteoporosis. The Dosing IntraVenous Administration (DIVA) study was designed to identify the optimal ibandronate IV injection schedule for the treatment of postmenopausal osteoporosis by comparing the efficacy and tolerability of 2- and 3-monthly injections with the previously evaluated daily oral ibandronate regimen. We report the effects on lumbar spine and proximal femur bone mineral density (BMD) and bone resorption markers over 2 years.

Methods. This randomized, double-blind, double-dummy, noninferiority study recruited 1395 women (aged 55–80 yrs; ≥ 5 yrs since menopause) with osteoporosis [mean lumbar spine (L2–L4) BMD T-score < -2.5 and ≥ -5.0]. Patients received IV ibandronate (2 mg every 2 mo or 3 mg every 3 mo) plus daily oral placebo, or 2.5 mg daily oral ibandronate plus 2- or 3-monthly IV placebo. Supplemental vitamin D (400 IU) and calcium (500 mg) were provided throughout the 2-year study.

Results. At 2 years, the 2- and 3-monthly IV regimens achieved statistically noninferior and also superior increases in lumbar spine BMD compared with the daily regimen (6.4% and 6.3% vs 4.8%, respectively; $p < 0.001$). Greater increases were also obtained with IV ibandronate versus daily in proximal femur BMD. Serum concentrations of the biochemical marker of bone resorption C-telopeptide of the alpha-chain of type I collagen were reduced to a similar extent in all treatment arms (53.4%–59.9%). The tolerability profile of the IV regimens was similar to that observed with daily oral therapy.

Conclusion. Ibandronate IV injections are an effective and well tolerated treatment for postmenopausal osteoporosis and provide a useful alternative to oral dosing. (J Rheumatol First Release Feb 1 2008)

Key Indexing Terms:

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Osteoporosis is a chronic, progressive disease that affects a substantial proportion of postmenopausal women¹. Treatment of osteoporosis and the need for care secondary to the condition, particularly with the rising average age of the population, place a considerable burden on healthcare services^{2,3}. Oral bisphosphonates produce clinically significant reductions in the risk of new vertebral and nonvertebral fractures⁴⁻⁸ and are currently the mainstay of treatment for osteoporosis. It is noted that much of the evidence supporting the efficacy of oral bisphosphonates in reducing the risk of nonvertebral fractures has been obtained in higher fracture-risk subgroups drawn from the overall study populations⁴⁻⁸. However, oral dosing may be contraindicated or unsuitable for some patients, e.g., those with gastrointestinal intolerance, those who have difficulties complying with the requisite procedures for oral dosing (fasting and posture), or those receiving multiple concomitant oral medications with similar requirements for fasting or early morning ingestion. Availability of an effective and well tolerated intravenous (IV) bisphosphonate provides a useful treatment alternative for these patients.

Ibandronate is a nitrogen-containing bisphosphonate that can be administered with extended between-dose intervals due to its potency and bone-binding characteristics^{9,10}. Oral ibandronate administered either daily or intermittently, with an extended between-dose interval of > 2 months, was reported to provide significant antifracture efficacy (3-year vertebral antifracture efficacy: 62% daily ibandronate; 50% intermittent ibandronate), along with a tolerability profile similar to that of placebo^{4,5}. Oral bisphosphonates have been shown to have similar bone mineral density (BMD) and biochemical bone marker effects between daily and weekly^{11,12} or monthly regimens¹³. Although etidronate, a non-nitrogen-containing bisphosphonate, has been reported to achieve a significant reduction in fracture risk with an extended between-dose interval, this was either in a subgroup population, with the addition of phosphate¹⁴, or when some data (Weeks 0–60 of 150 weeks on study drug) were excluded from the analysis¹⁵. Thus, the study of ibandronate was the first to show prospective, antifracture efficacy with a regimen other than daily in the entire preplanned study group⁴.

The high antiresorptive potency and good tolerability profile of ibandronate also enables administration by IV injection. Due to concerns regarding renal safety, other IV bisphosphonate formulations have been limited to lengthy infusions¹⁶. The short (15–30 s) ibandronate injection has not been associated with renal toxicity in patients with estimated glomerular filtration rate > 30 ml/minute and with no known diabetes mellitus or hypertension¹⁷⁻¹⁹. Pamidronate, used off-label, and zoledronate, recently licensed for the treatment of postmenopausal osteoporosis, are nitrogen-containing bisphosphonates administered via IV infusion over time periods of 15–30 minutes, if not longer.

The 2-year Dosing IntraVenous Administration (DIVA) study was initiated to identify the optimal IV ibandronate dos-

ing schedule by comparing the efficacy and safety of 2- and 3-monthly injections with the currently licensed daily oral regimen in women with postmenopausal osteoporosis. The 1-year results showed that both IV regimens were statistically noninferior, and indeed were superior to the daily oral regimen in increasing lumbar spine BMD ($p < 0.001$)¹⁸. Superior increases in proximal femur (total hip, femoral neck, and trochanter) BMD were also reported with the 3-monthly regimen ($p < 0.05$). Further, both IV ibandronate regimens were generally as well tolerated as daily oral ibandronate²⁰. The 2-year analysis has been completed to corroborate the results of the 1-year efficacy analysis and to provide more extensive safety and tolerability information for the IV regimens.

MATERIALS AND METHODS

Study design. DIVA was a randomized, double-blind, double-dummy, noninferiority study. A total of 58 centers in North America, Mexico, Europe, Australia, and South Africa participated in the recruitment of patients. The institutional review boards of each of the participating centers approved the study, which was conducted in accord with the principles of the Declaration of Helsinki and International Conference on Harmonization — Good Clinical Practice. All analyses requested by the authors were undertaken.

Study participants and medication. This study included postmenopausal women (aged 55–80 yrs; ≥ 5 yrs since menopause) with osteoporosis [mean lumbar spine (L2–L4) BMD T-score < -2.5 and ≥ -5.0 ; BMD was assessed in at least 2 vertebrae that were not affected by fracture or by any osteoarthritic process that might compromise accurate BMD measurement]; all patients provided written informed consent to participate. Women who had received oral bisphosphonates or any other drug affecting bone metabolism in the previous 6 months or who had previously received IV bisphosphonates at any time were excluded, as were those who had renal impairment (serum creatinine > 2.4 mg/dl, equivalent to 216 $\mu\text{mol/l}$), a history of major upper gastrointestinal disease, or allergy to bisphosphonates.

At enrollment, participants were randomized to receive one of 2 IV ibandronate regimens [2 mg every 2 mo (q2mo) or 3 mg every 3 mo (q3mo), plus daily oral placebo; annual cumulative exposure (ACE) 12 mg] or daily 2.5 mg oral ibandronate (plus IV placebo every 2 or 3 mo; ACE ~ 5.5 mg) in a 2:2:1 ratio. ACE is calculated based on the dose per administration \times doses per year \times bioavailability. The bioavailability of oral ibandronate from pharmacokinetic and mass balance studies is approximately 0.6%²¹, IV ibandronate bioavailability is 100%. Participants were instructed to take their oral medication after an overnight fast (≥ 6 h) and with 240 ml (8 oz) of plain water. Participants were then required to stay upright and fast for at least 60 minutes after oral dosing. Daily calcium (500 mg) and vitamin D (400 IU) supplements were also supplied to all participants.

To ensure comparable distribution of baseline BMD across the treatment arms, eligible participants were stratified by center and baseline lumbar spine BMD status prior to randomization. A centralized “call-in” system (Interactive Voice Response System, ClinPhone Ltd., Nottingham, England) was used to randomize patients to treatment.

Study endpoints

Primary efficacy endpoint. The primary efficacy endpoint was mean change (%) from baseline in lumbar spine (L2–L4) BMD after 1 year, measured by dual-energy x-ray absorptiometry (DEXA) as reported²⁰.

Secondary efficacy endpoints. Secondary efficacy endpoints included the mean change (%) from baseline in lumbar spine (L2–L4) BMD and proximal femur BMD after 2 years, measured by DEXA, using GE Lunar (Madison, WI, USA) and Hologic (Bedford, MA, USA) instruments. All reports were assessed by a central reading center (Synarc, Portland, OR, USA). Responder rates, defined as the proportion of patients (%) achieving changes in lumbar

spine and/or total hip BMD equal to or above baseline at 2 years, were calculated. As well, the proportion of patients achieving defined increases in lumbar spine ($\geq 6\%$) or total hip BMD ($\geq 3\%$), previously associated with vertebral²² and nonvertebral²³ antifracture efficacy, was prospectively evaluated.

The change (%) from baseline in serum concentrations of the biochemical marker of bone resorption C-telopeptide of the alpha-chain of type I collagen (sCTX) was assessed at 2, 4, 6, 12, and 24 months (2 mg q2mo) or at 3, 6, 12, and 24 months (3 mg q3mo). Blood samples for sCTX assessments were collected immediately before the scheduled IV or oral dose, after an overnight fast (≥ 6 h), and between 8:00 AM and 10:00 AM. The sCTX assays were analyzed at a central biomarker laboratory (Synarc, Lyon, France) with the appropriate quality controls to ensure between-run consistency.

Safety parameters. Adverse events were continuously monitored throughout the 2-year study period. Clinical vertebral and nonvertebral fractures were reported as adverse events and confirmed radiographically. Laboratory safety parameters, including serum creatinine concentrations, were assessed at screening and then every 3 or 4 months (depending upon the dosing schedule), immediately before the next scheduled IV dose. Clinically relevant changes in serum creatinine were defined as an increase from baseline of ≥ 0.5 mg/dl (if baseline creatinine < 1.4 mg/dl) or ≥ 1 mg/dl (if baseline creatinine ≥ 1.4 mg/dl) or a 2-fold increase during treatment. Creatinine clearance was calculated using the Cockcroft-Gault formula²⁴.

Statistical analysis. Analysis populations: intent-to-treat (ITT) populations are generally considered more variable than per-protocol (PP) populations, as they can include patients who do not directly follow the protocol, and who, consequently, may reduce the detectable treatment effect. In accord with clinical trial guidelines²⁵, the PP population was therefore used for the primary analysis of the efficacy endpoints in this active-comparator study. Confirmatory analyses were performed using the ITT population.

The ITT population comprised all patients who received at least one dose of study medication and reported at least one efficacy datapoint (BMD or sCTX). The PP population included all patients in the ITT population who had no protocol violations at baseline or during the study (Figure 1). Protocol violations were categorized as follows: biased (BMD measurements reported off-treatment) baseline or followup BMD assessment; baseline T-score ≥ -2.5 SD; excluded concomitant disease at baseline or developed during Year 1 of study; prohibited medication use; vitamin D deficiency at screening (serum 25-hydroxy vitamin D < 10 ng/ml, equivalent to 24 nmol/l); lack of compliance with treatment regimens ($< 75\%$ medication taken); or unconfirmed menopausal status. The safety population comprised all patients who received at least one dose of trial medication, including those withdrawn prematurely, and who had at least one followup datapoint.

Analysis of the primary efficacy parameter at 2 years and secondary efficacy endpoints. At 2 years, the changes (%) from baseline in lumbar spine BMD provided by the 2 mg q2mo and 3 mg q3mo IV regimens were compared with the established daily oral regimen by noninferiority test. For all efficacy analyses, results from the daily oral ibandronate arms were pooled. Noninferiority margins for the analysis of change (%) from baseline in lumbar spine BMD were based on 30% of the minimum treatment effect observed between daily oral ibandronate and placebo after 2 years in a prior clinical study⁴. Thus, noninferiority would be concluded if the lower boundary of the 2-sided 95% confidence interval (95% CI) for the difference in the means between the IV regimens and oral daily regimen was $\geq -1.3\%$ at 2 years. Noninferiority was assessed using analysis of variance (ANOVA), controlling for geographic location and baseline lumbar spine L2–L4 BMD.

Following demonstration of noninferiority for the primary efficacy parameter, superiority of the IV regimens to the daily regimen was tested using the ANOVA model. Summary statistics were produced for the changes (%) from baseline in proximal femur BMD and sCTX, with 95% CI for the difference in the mean BMD and median sCTX values between each IV regimen and the daily regimen being calculated.

Analysis of safety variables. All adverse events reported during the 2-year study period were assessed in the safety analysis. Adverse events were evaluated by standardized tabulation of the frequency and incidence rates (on a

per-patient basis). Laboratory abnormalities were reported by individual listings. Safety data from the 2 groups receiving daily oral ibandronate were pooled and the 2 active IV regimens were considered separately.

RESULTS

Patient disposition and baseline characteristics. A total of 1395 postmenopausal women were randomized into the study²⁰ (Figure 1); of these, 1117 patients completed 2 years, i.e., 265 (19.0%) withdrew from the study. The PP population included 1089 women (2 mg q2mo, $n = 350$; 3 mg q3mo, $n = 364$; and 2.5 mg daily, $n = 375$). The main reasons for exclusion from the PP population were noncompliance with the daily regimen ($\sim 18\%$), noncompliance with the IV regimens ($\sim 12\%$), and no reliable BMD values ($\sim 5\%$). Year 2 visit data were censored for partial noncompliance with the daily ($\sim 8\%$) or IV regimens ($\sim 4\%$) and the taking of prohibited medications ($\sim 1\%$). The number of patients excluded from the PP analysis was similar across the treatment groups; for the analysis of bone turnover, incorrect sCTX sampling excluded 15%–18%. A total of 1358 patients (2 mg q2mo, $n = 442$; 3 mg q3mo, $n = 459$; and 2.5 mg daily, $n = 457$) and 1382 patients (2 mg q2mo, $n = 448$; 3 mg q3mo, $n = 469$; and 2.5 mg daily, $n = 465$) were included in the ITT and safety populations, respectively. For all criteria, baseline patient characteristics and demographics were well balanced across the treatment groups (Table 1).

Efficacy analysis

Lumbar spine BMD. At 2 years, greater mean increases in lumbar spine BMD were observed in the 2 mg q2mo and 3 mg q3mo IV arms [6.4% (95% CI 5.9, 6.9; $n = 320$) and 6.3% (95% CI 5.7, 6.8; $n = 334$), respectively] than in the daily arm [4.8% (95% CI 4.3, 5.4; $n = 334$)] (Figure 2A). For each comparison of IV ibandronate versus oral dose, the lower boundary of the 2-sided 95% CI for the between-group difference was greater than the prespecified margin (-1.3%), thus confirming noninferiority (Figure 3).

Additionally, the 2 mg q2mo and 3 mg q3mo IV regimens were superior to the daily oral regimen (prospectively planned statistical analyses, ANOVA). There was no difference between the 2 IV regimens. Using the ITT population, the IV arms were again noninferior and indeed were superior to the daily oral arm [2 mg q2mo, 6.0% (95% CI 5.5, 6.5; $n = 389$); 3 mg q3mo, 5.8% (95% CI 5.3, 6.2; $n = 413$); and daily, 4.6% (95% CI 4.1, 5.1; $n = 422$); $p < 0.001$ for both IV regimens compared with daily] (Figure 2B).

Proximal femur BMD. Increases in proximal femur BMD (total hip, femoral neck, trochanter) were similar in the 2 IV arms and both were superior to the daily oral regimen for gains in total hip and trochanter BMD at 2 years (post hoc analysis: $p < 0.001$ vs daily for all comparisons, and noninferior for femoral neck; Figure 2A). Comparable findings were reported for the ITT analysis (Figure 2B).

Responder analyses of lumbar spine and total hip BMD. For

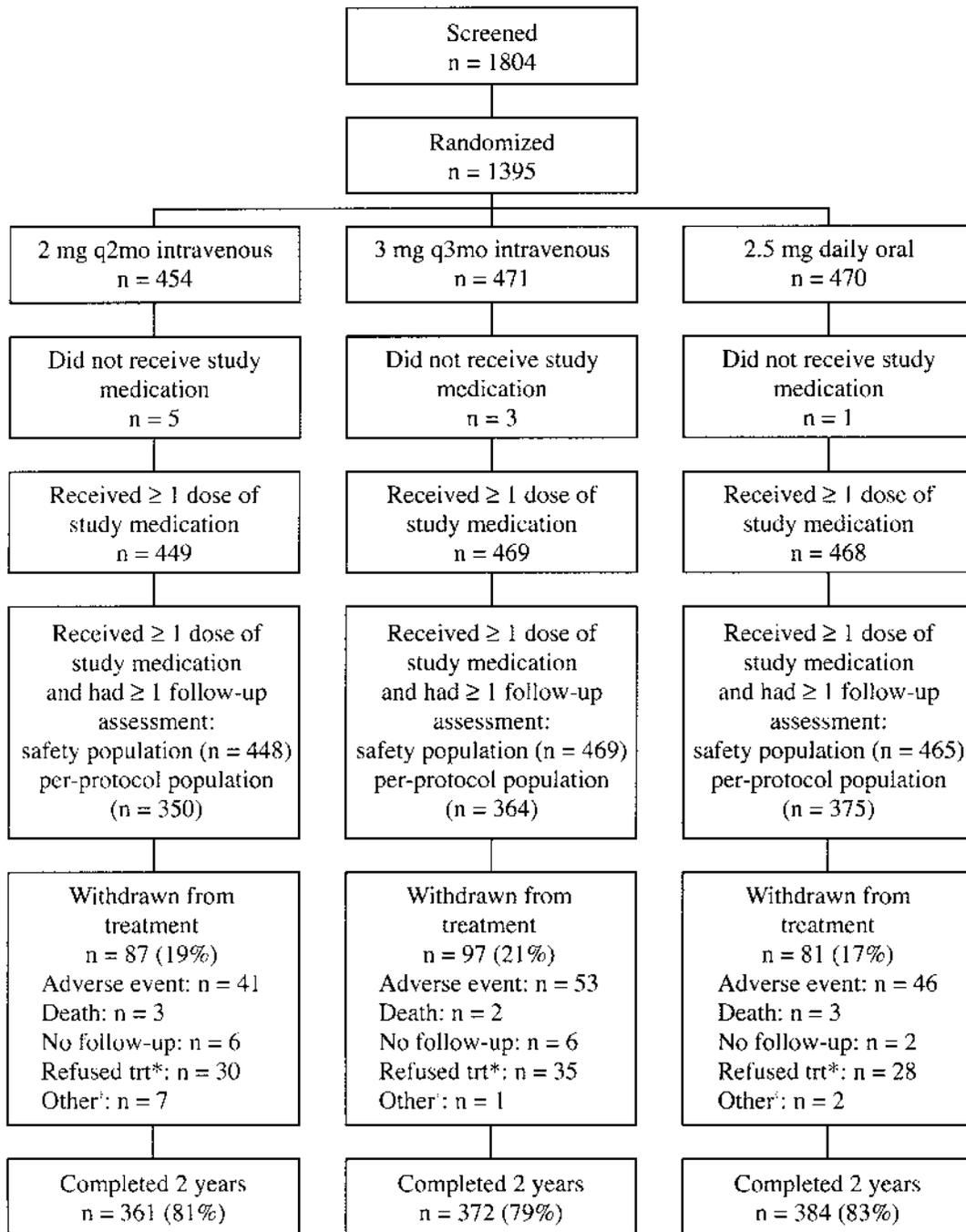


Figure 1. Patient disposition and outcomes. trt: treatment. *Includes “did not cooperate” and “withdrew consent.” †Includes “insufficient therapeutic response,” “early improvement,” “violation of selection criteria at entry,” and “other protocol violation.”

all BMD responder analyses, a significantly greater proportion of patients (PP population) in the IV arms achieved increases in BMD above baseline at the lumbar spine and total hip and at both sites combined compared with the daily arm (Table 2). In the same population, more patients in the IV arms achieved $\geq 6\%$ increase in lumbar spine BMD and $\geq 3\%$ increase in total hip BMD than those receiving daily ibandronate (Table 2).

In the ITT population, more patients achieved increases in lumbar spine BMD in the IV arms than the daily arm (90.5% in q2mo arm and 89.8% in q3mo arm, vs 82.9% in the daily arm; $p \leq 0.004$ for both comparisons). Similarly, more patients in the IV arms achieved increases in total hip BMD compared with the daily arm (84.4% in q2mo arm and 81.7% in q3mo arm, vs 74.4% in the daily arm; $p \leq 0.011$ for both comparisons). Also, an increase in both lumbar spine and total

Table 1. Baseline demographics. Data are mean (SD); per-protocol population.

	2 mg q2mo Ibandronate, n = 350*	3 mg q3mo Ibandronate, n = 364*	2.5 mg daily Ibandronate, n = 375*
Age, yrs	66.5 (6.2)	65.6 (6.2)	65.6 (6.1)
Weight, kg	64.1 (10.7)	64.0 (10.5)	63.5 (11.1)
Height, cm	157.9 (6.3)	158.1 (7.0)	158.4 (6.5)
BMI, kg/cm ²	25.7 (4.0)	25.6 (4.3)	25.3 (4.3)
Lumbar spine (L2–L4) BMD, g/cm ²	0.75 (0.07)	0.74 (0.07)	0.75 (0.07)
Lumbar spine (L2–L4) BMD, T score	–3.28 (0.56)	–3.29 (0.58)	–3.26 (0.53)
Total hip BMD, g/cm ²	0.74 (0.10)	0.73 (0.10)	0.74 (0.10)
Total hip BMD, T score**	–1.91 (0.87)	–1.99 (0.86)	–1.98 (0.87)
Previous fracture, % ***	41.8	42.9	44.4
sCTX, ng/ml†	0.49 (0.01–1.72)	0.49 (0.04–1.93)	0.51 (0.10–2.20)
25-OH-D, ng/ml	25.1 (9.5)	24.3 (8.9)	24.7 (9.2)

* n = overall per-protocol population, numbers vary slightly for individual measures. ** NHANES III adjusted. *** Since age 45 years. † Median (range) values. q2mo: every 2 months. q3mo: every 3 months. BMD: bone mineral density. sCTX: serum concentrations of the biochemical marker of bone resorption C-telopeptide of the alpha-chain of type I collagen.

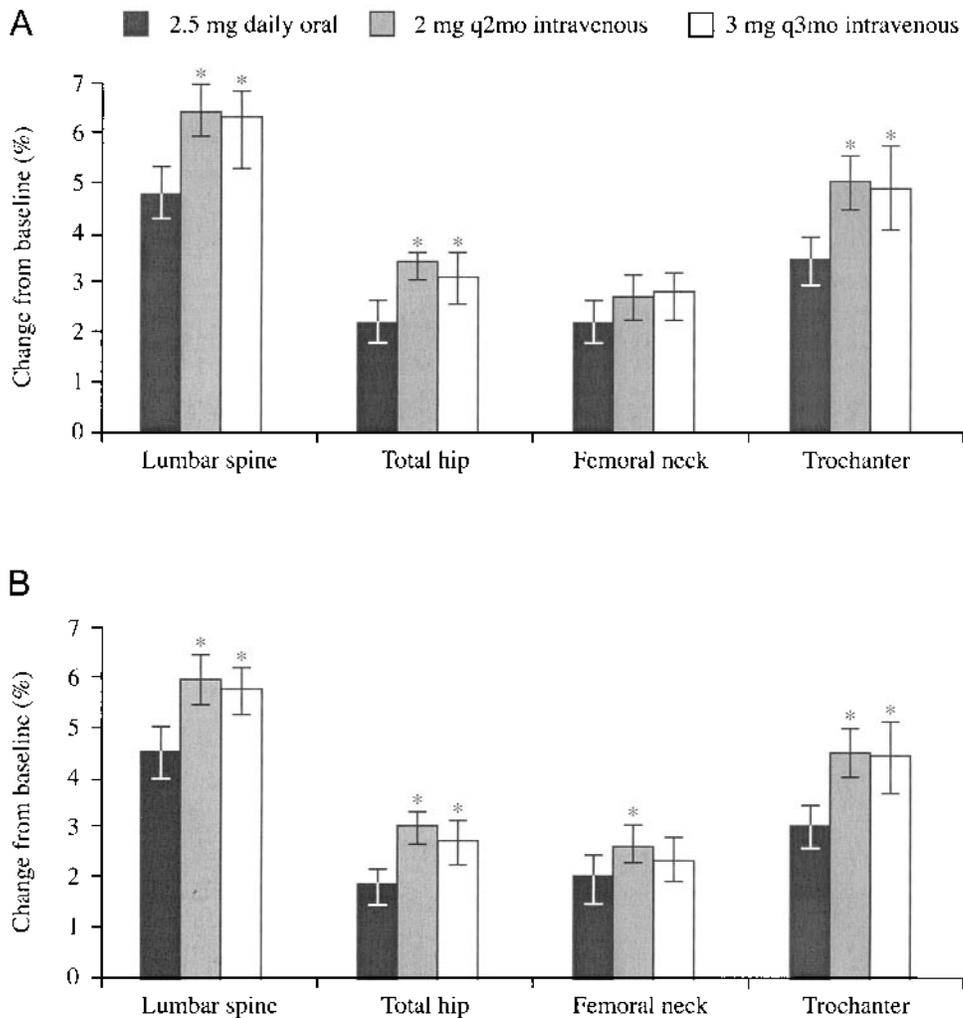


Figure 2. Mean change (percentage, 95% CI) from baseline in lumbar spine and proximal femur BMD after 2 years. A. Per-protocol population. *p < 0.001 vs 2.5 mg daily ibandronate. B. Intent-to-treat population. q2mo: every 2 months; q3mo: every 3 months. *p < 0.05 vs 2.5 mg daily ibandronate.

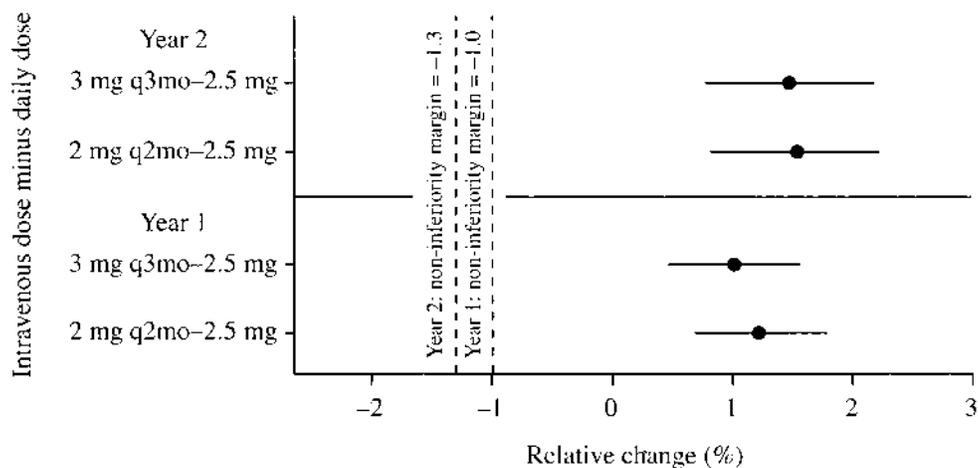


Figure 3. Noninferiority analysis of mean change (%) from baseline in lumbar spine BMD (L2-L4) after 2 years (per-protocol). q2mo: every 2 months; q3mo: every 3 months.

Table 2. Patients (%; per-protocol population) with lumbar spine and total hip BMD increases above baseline or predefined levels (6% and 3%) following 2 years of treatment with ibandronate.

	2 mg q2mo Ibandronate, n = 375*	3 mg q3mo Ibandronate, n = 350*	2.5 mg daily Ibandronate, n = 364*
Patients (%) with BMD increases > baseline			
Lumbar spine	92.8 [†]	92.8 [†]	84.7
Total hip	88.6 ^{††}	85.6 ^{††}	77.0
Lumbar spine and total hip	83.1 [†]	80.1 [†]	68.8
Patients (%) with lumbar spine BMD ≥ 6%	53.1 [§]	49.4 [§]	37.7
Patients (%) with total hip BMD ≥ 3%	56.3 ^{**}	49.8 ^{**}	40.3

* n = overall per-protocol population, numbers vary slightly for individual measures. [†] p ≤ 0.001 vs 2.5 mg daily ibandronate. ^{††} p ≤ 0.004 vs 2.5 mg daily ibandronate. [§] p ≤ 0.002 vs 2.5 mg daily ibandronate. ^{**} p ≤ 0.014 vs 2.5 mg daily ibandronate. BMD: bone mineral density. q2mo: every 2 months. q3mo: every 3 months.

hip BMD was achieved in a greater proportion of patients receiving IV versus daily oral ibandronate (2 mg in q2mo, 78.6%; 3 mg in q3mo, 75.3%; and daily, 66.3%; p ≤ 0.004 for both comparisons).

For the other ITT analyses, more patients in the IV arms had increases ≥ 6% in lumbar spine BMD or ≥ 3% in total hip BMD than patients in the daily arm (lumbar spine BMD 2 mg in q2mo, 49.6%; 3 mg in q3mo, 45.5%; and daily, 35.8%; p ≤ 0.004 for both comparisons. Total hip BMD 2 mg in q2mo, 52.2%; 3 mg in q3mo, 46.6%; and daily, 37.1%; p ≤ 0.006 for both comparisons).

sCTX. Decreases in sCTX observed in all treatment arms within 3 months of treatment initiation were maintained throughout the study (Figure 4). The decreases in sCTX reported after 2 years were 55.6%, 53.4%, and 59.9% in the 2 mg q2mo, 3 mg q3mo, and daily arms, respectively, in the PP population (Figure 4A); and 56.1%, 51.7%, and 58.6% in the 2 mg q2mo, 3 mg q3mo, and daily arms, respectively, in the ITT population (Figure 4B). Levels of sCTX in the IV arms

represent the residual suppression levels at the end of the 2- or 3-month dosing interval.

Safety parameters. All safety analyses are based on data collected throughout the 2-year study period. The overall incidence of adverse events, drug-related adverse events, and drug-related adverse events leading to withdrawal was similar across all treatment groups (Table 3). The most commonly reported adverse events, regardless of relationship to treatment, were back pain, arthralgia, and nasopharyngitis; these occurred with consistent frequency across the 3 treatment groups. No cases of osteonecrosis of the jaw or related dental problems were reported. The number of observed serious adverse events was similar in all 3 treatment arms (proportion of patients, daily, 14.4%; 2 mg q2mo, 16.3%; and 3 mg q3mo, 13.2%). Only 11 serious adverse events considered related to study medication were reported during the 2-year study period (Table 4). In total, 9 deaths were reported, 4 during the first year and 5 during the second year, one of which occurred after the end of the followup period (aortic dissection; Table 4). No

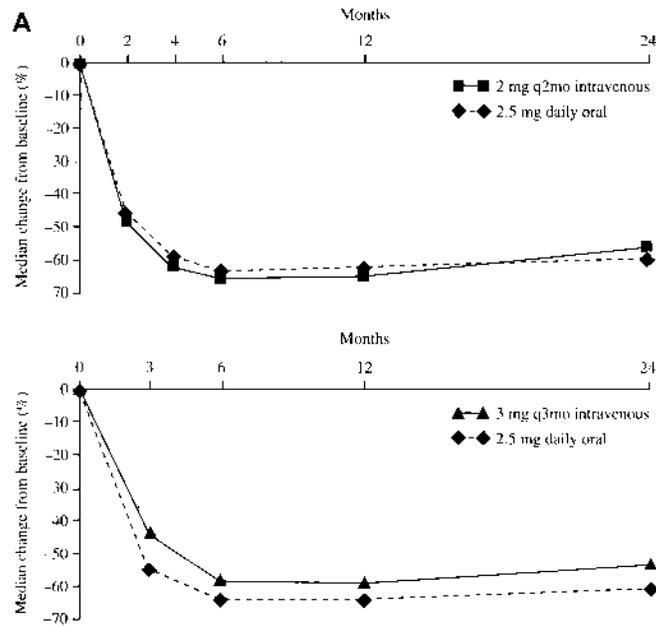


Figure 4A. Median change (%) from baseline in sCTX. Per-protocol population. Top panel: Data are residual levels of sCTX at the end of each dosing period for 2 mg q2mo ibandronate (per-protocol population; n = 342 and 360 at 12 months, and n = 301 and 310 at 24 months for 2 mg q2mo arm and 2.5 mg daily arm, respectively). Bottom panel: Data are residual levels of sCTX at the end of each dosing period for 3 mg q3mo ibandronate (per-protocol population; n = 347 and 360 at 12 months, and n = 298 and 310 at 24 months for 3 mg q3mo arm and 2.5 mg daily arm, respectively). sCTX: serum concentrations of the biochemical marker of bone resorption C-telopeptide of the alpha-chain of type I collagen. q2mo: every 2 months. q3mo: every 3 months.

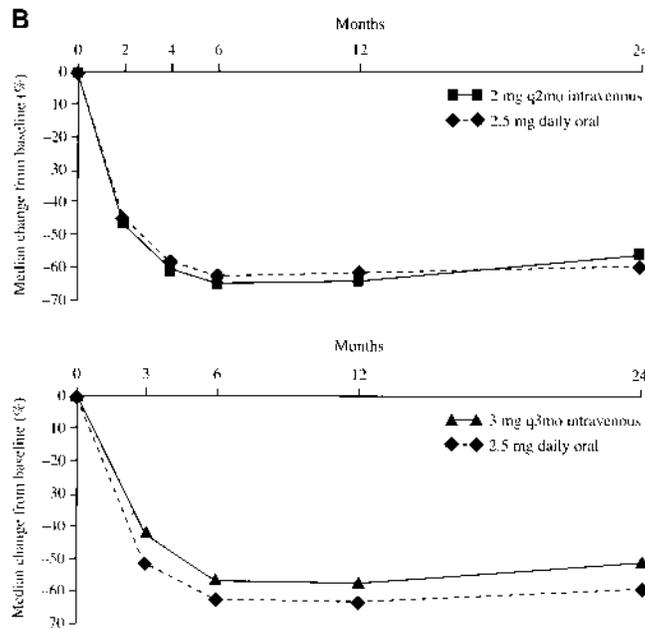


Figure 4B. Median change (%) from baseline in sCTX. Intent-to-treat (ITT) population. Top panel: Data are residual levels of sCTX at the end of each dosing period for 2 mg q2mo ibandronate (ITT population; n = 385 and 414 at 12 months, and n = 363 and 386 at 24 months for 2 mg q2mo arm and 2.5 mg daily arm, respectively). Bottom panel: Data are residual levels of sCTX at the end of each dosing period for 3 mg q3mo ibandronate (ITT population; n = 399 and 414 at 12 months, and n = 373 and 386 at 24 months for 3 mg q3mo arm and 2.5 mg daily arm, respectively). sCTX: serum concentrations of the biochemical marker of bone resorption C-telopeptide of the alpha-chain of type I collagen. q2mo: every 2 months. q3mo: every 3 months.

Table 3. Overall summary of safety (safety population; %).

	2 mg q2mo Ibandronate, n = 448	3 mg q3mo Ibandronate, n = 469	2.5 mg daily Ibandronate, n = 465
Overall			
Any adverse event	88.6	85.3	87.7
Any drug-related adverse event	46.4	42.0	36.8
Any drug-related adverse event leading to withdrawal	6.5	7.7	6.0
Any serious adverse event	16.3	13.2	14.4
Any drug-related serious adverse event	1.1	0.4	0.9
Any drug-related serious adverse event leading to withdrawal, n (%)	3 (0.7)	0	2 (0.4)
Death, n (%)	3 (< 1)	2 (< 1)	4 (< 1)*
Adverse events of special interest			
Renal, n (%)	20 (4.5)	15 (3.2)	18 (3.9)
Clinical osteoporotic fractures, n (%)	21 (4.7)	23 (4.9)	29 (6.2)

* Includes one patient who died of aortic dissection after the end of the followup period; this event was not considered related to study drug. q2mo: every 2 months. q3mo: every 3 months.

Table 4. Serious adverse events and deaths (safety population).

Drug-related serious adverse events	Detail
2 mg q2mo ibandronate, n = 448	Gastric ulcer, gastrointestinal ulcer, anemia, increased hepatic enzyme, polymyalgia rheumatica
3 mg q3mo ibandronate, n = 469	Gastritis (2 incidents)
2.5 mg daily ibandronate, n = 465	Melena, esophageal ulcer, drug hypersensitivity, temporal arteritis
Deaths	
2 mg q2mo ibandronate, n = 448	Acute pancreatitis, myocardial infarction, and pulmonary embolism
3 mg q3mo ibandronate, n = 469	Myocardial infarction (2 incidents)
2.5 mg daily ibandronate, n = 465	Pulmonary edema, gallbladder cancer, ventricular arrhythmia and aortic dissection*

* Occurred after the end of the followup period. q2mo: every 2 months. q3mo: every 3 months.

death was considered related to study treatment as predisposing conditions and/or confounding factors were present in all patients. Similar proportions of patients in each group withdrew from the study (17%–21%; Figure 1). The number of patients withdrawing due to an adverse event (including death) was comparable for the 3 treatment groups (9.8% in 2 mg q2mo, 11.7% in 3 mg q3mo, and 10.5% in the daily oral arm).

Flu-like illness, a combination of the investigator-reported adverse event terms “influenza-like illness” and “acute-phase reaction,” was observed with a similar frequency in the IV groups and was higher than in the daily group (5.6% in 2 mg q2mo and 4.9% in 3 mg q3mo groups vs 1.5% with daily). A lower frequency of flu-like illness was observed in a more limited analysis that considered the typical onset (within 3 days of dosing) and duration (< 7 days) of events (4.0% in the 2 mg q2mo arm and 3.8% in the 3 mg q3mo arm vs 0.9% in the daily arm). A further exploratory analysis evaluated a wide range of symptoms (n = 33) that could potentially indicate a reaction to IV dosing. These included both specific (e.g., influenza-like illness, acute-phase reaction, myalgia, and

arthralgia) and nonspecific (e.g., headache, dizziness, fatigue, malaise, and “feeling hot”) adverse event terms (data reported consider the typical onset and duration of events likely to be associated with IV administration). The rate of adverse events included within this general analysis of flu-like symptoms was 15.6% in the 2 mg q2mo arm, 10.0% in the 3 mg q3mo arm, and 4.3% in the daily arm. In this exploratory analysis, the incidence of specifically diagnosed and reported influenza-like illness, acute-phase reaction, myalgia, and arthralgia was low ($\leq 3.6\%$, 0.4% , $\leq 2.9\%$, and 1.3% in the IV arms and 0.9% , 0% , 0.4% , and 0% in the daily arm, respectively). Symptoms were generally mild to moderate in intensity, transient, and mostly associated with the first administration only, and caused few withdrawals (0.4% – 2.8% in all dosing arms).

The incidence of renal adverse events was similar across the treatment groups (Table 3). No case of acute renal failure was reported. Estimated baseline creatinine clearance was < 90 ml/minute in virtually all and 60 to < 90 ml/minute or 30 to < 60 ml/minute in the majority of participants; only 6 participants had an estimated baseline creatinine clearance < 30 ml/minute. The proportion of participants with any decrease

in creatinine clearance (at any timepoint) was similar among the treatment groups: 21%, 23%, and 21% in the 2 mg q2mo, 3 mg q3mo, and daily oral arms, respectively. After 2 years of treatment, 12 participants from the 3 treatment groups (6 patients during the first year and an additional 6 patients during Year 2) had clinically relevant changes in serum creatinine; all had concomitant conditions or treatments potentially contributing to the increase in serum creatinine and no incident was considered drug-related.

After 2 years, the incidence of clinical osteoporotic fractures (including fractures of the vertebrae, clavicle, scapula, ribs, pelvis, sternum, humerus, forearm, femur, patella, tibia, fibula, ankle, and carpus) was similar in the IV groups, 4.7% and 4.9% in the 2 mg q2mo and 3 mg q3mo arms, respectively; and slightly, but not significantly, lower than in the daily arm, 6.2% (Table 3).

DISCUSSION

The DIVA study compared, at 1 and 2 years, the efficacy and safety of 2 mg q2mo and 3 mg q3mo IV ibandronate injection regimens (providing the same annual cumulative exposure, 12 mg) with the daily oral ibandronate regimen, reported to be effective versus placebo in postmenopausal women with osteoporosis⁴. The primary endpoint of this randomized, double-blind, noninferiority study had been achieved at 1 year, in that both IV regimens were proven to be at least noninferior, and even superior, to the daily oral regimen for change (%) from baseline in lumbar spine BMD²⁰. The aim of the 2-year analysis was to substantiate the 1-year efficacy and safety findings, and to provide longer-term data on the IV regimens in the treatment of postmenopausal osteoporosis.

The 2-year analysis extends the 1-year results: both IV regimens achieved similar increases in lumbar spine BMD that were greater than that with the daily oral regimen. Prespecified noninferiority analyses confirmed that both IV regimens were as effective as the daily regimen. Additionally, both IV regimens were prospectively shown to be superior to the daily oral regimen in terms of gains in lumbar spine BMD ($p < 0.001$). The increases noted in proximal femur BMD (total hip, femoral neck, and trochanter) by the end of the 2-year study period generally supported the findings at the lumbar spine, although superiority was not statistically significant at the femoral neck. The greater increases in BMD associated with the IV regimens are mirrored in the responder analyses. A significantly larger proportion of women responded to IV ibandronate treatment, achieving increases above baseline in lumbar spine BMD or total hip BMD or both lumbar spine and total hip BMD ($p \leq 0.011$). At the studied doses, the intermittent IV ibandronate injection regimens and daily oral ibandronate also provided similar decreases throughout the 2-year study period in the biochemical marker of bone resorption, sCTX.

Overall, the tolerability profile for the intermittent IV ibandronate injection regimens was similar to daily oral iban-

dronate, which was previously shown to have a tolerability profile comparable with placebo⁴. At 2 years, there were no imbalances between the 3 treatment groups in the number of adverse events reported. The reported incidences of flu-like illness were generally of short duration and mild to moderate in intensity. These events occurred within the first days after administration, resolved spontaneously or following administration of antipyretics, and recurred in only a few cases. In contrast with other IV bisphosphonates²⁶⁻²⁸, no renal safety concerns were reported with IV ibandronate, consistent with previous reports^{17,18,29-31}.

In these 2-year findings of the treatment of postmenopausal osteoporosis, IV ibandronate injections (2 mg q2mo and 3 mg q3mo) were at least as effective as the daily oral ibandronate regimen and were similarly well tolerated. Intravenous ibandronate injections therefore offer an effective treatment option for those patients in whom oral administration is unsuitable. The efficacy and tolerability profiles of both IV ibandronate regimens were similar and the 3 mg quarterly injection regimen could provide an advantage in terms of convenience to the patient and medical staff over the 2 mg q2mo regimen.

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