

# Intravenous Ibandronate Injections in Postmenopausal Women With Osteoporosis

## One-Year Results From the Dosing Intravenous Administration Study

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**Objective.** Although oral bisphosphonates are effective treatments for postmenopausal women with osteoporosis, oral dosing may be unsuitable for some patients. An efficacious intravenously administered bisphosphonate could be beneficial for such patients. Ibandronate, a potent nitrogen-containing bisphosphonate, can be administered using extended dosing inter-

vals, either orally or by rapid intravenous injection. The aim of this study was to identify the optimal intravenous dosing regimen for ibandronate in postmenopausal women with osteoporosis.

**Methods.** In a randomized, double-blind, double-dummy, phase III, noninferiority study, we compared 2 regimens of intermittent intravenous injections of ibandronate (2 mg every 2 months and 3 mg every 3 months) with a regimen of 2.5 mg of oral ibandronate daily, the latter of which has proven antifracture efficacy. The study group comprised 1,395 women (ages 55–80 years) who were at least 5 years postmenopausal. All patients had osteoporosis (lumbar spine [L2–L4] bone mineral density [BMD] T score less than –2.5). Participants also received daily calcium (500 mg) and vitamin D (400 IU). The primary end point was change from baseline in lumbar spine BMD at 1 year. Changes in hip BMD and in the level of serum C-telopeptide of type I collagen (CTX) were also measured, as were safety and tolerability.

**Results.** At 1 year, mean lumbar spine BMD increases were as follows: 5.1% among 353 patients receiving 2 mg of ibandronate every 2 months, 4.8% among 365 patients receiving 3 mg of ibandronate every 3 months, and 3.8% among 377 patients receiving 2.5 mg of oral ibandronate daily. Both of the intravenous regimens not only were noninferior, but also were superior ( $P < 0.001$ ) to the oral regimen. Hip BMD increases (at all sites) were also greater in the groups receiving medication intravenously than in the group receiving ibandronate orally. Robust decreases in the serum CTX level were observed in all arms of the study.

Supported by F. Hoffmann-La Roche Ltd, Basel, Switzerland, and GlaxoSmithKline, Brentford, UK.

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Dr. Delmas has received consulting fees and/or honoraria from the following pharmaceutical companies: Amgen, Eli Lilly, GlaxoSmithKline, Novartis, Nycomed, Organon, Pfizer, Proctor & Gamble, Sanofi-Aventis, Servier, Wyeth (less than \$10,000 each), and Roche (more than \$10,000). Drs. Reginster, Civitelli, and Reid have received consulting fees and/or honoraria (less than \$10,000 each) from Roche and GlaxoSmithKline.

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Submitted for publication July 13, 2005; accepted in revised form March 15, 2006.

**Both of the intravenous regimens were well tolerated and did not compromise renal function.**

**Conclusion.** As assessed by BMD, intravenous injections of ibandronate (2 mg every 2 months or 3 mg every 3 months) are at least as effective as the regimen of 2.5 mg orally daily, which has proven antifracture efficacy, and are well tolerated.

Oral bisphosphonates are the current mainstay of treatment for postmenopausal osteoporosis. Results of several large clinical trials attest to the efficacy of oral bisphosphonates in reducing fracture risk (1–6) as well as their favorable safety and tolerability profile (1–9). However, oral administration may be unsuitable in some populations, such as patients with gastrointestinal (GI) intolerance or those with difficulty complying with the requisite procedures for oral dosing (e.g., patients with cognitive impairment or those receiving several other oral medications). Oral dosing is also contraindicated in some patients (e.g., those with abnormalities of the esophagus that delay esophageal emptying). The additional availability of an intravenous (IV) bisphosphonate preparation could therefore be clinically advantageous for use in such patients.

Ibandronate is a nitrogen-containing bisphosphonate, the potency of which (10), combined with its favorable tolerability (1) and bone-binding characteristics (11), allow it to be administered orally, using extended dosing intervals. In a study of 2,946 postmenopausal women with osteoporosis, oral ibandronate given daily or intermittently (between-dose interval of >2 months) produced substantial antifracture efficacy; the reductions in vertebral fracture risk at 3 years were 52% (daily dosing) and 50% (intermittent dosing), and both regimens were well tolerated, with a safety profile similar to that of placebo (1,2). At 1 year, relative risk reductions of 58% and 59% were observed for new morphometric and combined new moderate and severe vertebral fractures, respectively (1,12). When given as a once-monthly regimen, oral ibandronate was at least as effective (as measured by increases in bone mineral density [BMD]) as the daily regimen, with similar tolerability (13).

Because ibandronate is a highly potent inhibitor of bone resorption (10), it can also be administered as a rapid IV injection over 15–30 seconds, with extended dose-free intervals. When given once every 3 months, IV ibandronate produced dose-dependent and clinically meaningful increases in BMD and decreases in the levels of biochemical markers of bone turnover in postmenopausal women with osteoporosis (14,15). The same

regimen also significantly reduced vertebral fracture risk in patients with corticosteroid-induced osteoporosis (16). In those 3 studies, IV ibandronate was well tolerated, with a safety profile similar to that of placebo, and, notably, no indications of renal toxicity were observed.

To identify the optimal IV dosing regimen for ibandronate in postmenopausal women with osteoporosis, the Dosing IntraVenous Administration (DIVA) study was initiated to compare the efficacy and safety of IV ibandronate administered every 2 months or every 3 months with the efficacy and safety of the approved regimen of 2.5 mg of ibandronate administered orally. The principal hypothesis for the DIVA study was that the efficacy of the 2 IV regimens would be noninferior to the daily oral regimen after 12 months of treatment. The study is continuing (in a blinded manner) for an additional 12 months, at which point a confirmatory analysis will be performed.

## PATIENTS AND METHODS

**Role of the funding source.** This research was supported by F. Hoffmann-La Roche Ltd and GlaxoSmithKline. F. Hoffmann-La Roche and GlaxoSmithKline had a role in study design, and in data analysis and interpretation but not in data collection. All authors contributed to the manuscript and approved the content prior to submission. F. Hoffmann-La Roche Ltd supplied the study drug.

**Study participants.** Women ages 55–80 years who were at least 5 years postmenopausal and who had osteoporosis (mean lumbar spine [L2–L4] BMD T score less than –2.5 but greater than or equal to –5.0) were screened for eligibility. Women who had previously received IV bisphosphonates at any time or who, in the previous 6 months, had received oral bisphosphonates or any other drug affecting bone metabolism were excluded, as were those who had renal impairment (serum creatinine level >2.4 mg/dl), a history of major upper GI disease, or allergy to bisphosphonates.

**Study design and treatments.** DIVA is a 2-year, randomized, double-blind, double-dummy, phase III, noninferiority study involving 58 centers in the US, Canada, Mexico, Europe, Australia, and South Africa. The study protocol was approved by local ethics committees at all centers, and all patients gave written informed consent. The study conformed in full with the principles of the Declaration of Helsinki and was conducted according to the requirements of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (<http://www.ich.org/LOB/media/MEDIA482.pdf>).

Eligible participants were randomly allocated in a 2:2:1:1 ratio to 1 of 4 treatment regimens for 2 years, as follows: 2 mg of ibandronate administered IV every 2 months plus daily oral placebo (every-2-months group), 3 mg of ibandronate administered IV every 3 months plus daily oral placebo (every-3-months group), 2.5 mg of oral ibandronate daily plus placebo administered IV every 2 months, or 2.5 mg

of oral ibandronate daily plus placebo administered IV every 3 months (oral-treatment groups). The cumulative annual dose of ibandronate (12 mg) was the same for both of the investigational IV regimens. Treatment allocation was performed via a centralized call-in system (Interactive Voice Response System; ClinPhone Ltd, Nottingham, UK); allocation to treatment included stratification of patients by center and baseline lumbar spine BMD reading, to ensure similar distribution across the treatment groups.

Participants were instructed to take their oral medication after an overnight fast ( $\geq 6$  hours) with 240 ml (8 oz) of plain water and to maintain an upright posture and fasting state for at least 60 minutes after dosing. Each IV injection was given over 15–30 seconds. All patients received supplementary oral calcium (500 mg/day) and vitamin D (400 IU/day), both of which were taken in the evening. During the study period, patients were not allowed to take any other bisphosphonate or any drug affecting bone metabolism.

**Assessments. Primary efficacy parameter.** The primary efficacy parameter was the mean (%) change from baseline at 1 year in the BMD of at least 2 vertebrae in the lumbar spine (L2–L4) that were not fractured or so affected by degenerative changes that accurate measurement would be jeopardized. BMD was measured by dual x-ray absorptiometry (DXA) scanning (Hologic [Bedford, MA] or GE Lunar [Madison, WI] instruments), and scans were read at a central reading center (Synarc, Portland, OR). Scanners were cross calibrated by circulating cross-calibration phantoms (overall, 23% of scanners required adjustments ranging from 1% to 5%). The longitudinal precision or stability of each DXA scanner was monitored, and calibration was performed by establishing a longitudinal instrument quality control correction factor for each study center. Coefficients of variation were below longitudinal quality control reference values (0.5% for Hologic and 0.6% for GE Lunar) for all but 5 scanners (longitudinal correction of BMD measurements was required in 2 cases). For 8 scanners, patient BMD results were adjusted to remove the effect of a small but significant linear drift in calibration.

**Secondary efficacy parameters.** The mean (%) change from baseline in BMD of the proximal femur (total hip, femoral neck, and hip trochanter) after 1 year was predefined as a secondary efficacy parameter, as were BMD responder rates, defined as the proportion (%) of participants whose lumbar spine and/or total hip BMD measurements were greater than or equal to the baseline measurements at 1 year.

The other efficacy parameter analyzed was the median (%) change from baseline in serum levels of C-telopeptide of type I collagen (CTX), a biochemical marker of bone resorption, at 2, 4, 6, and 12 months for patients assigned to the every-2-months dosing schedule and at 3, 6, and 12 months for those assigned to the every-3-months schedule. Blood samples for the assessment of serum CTX were collected just before the scheduled IV or oral dose, after an overnight fast ( $\geq 6$  hours), between 8:00 AM and 10:00 AM. Serum CTX levels measured in the 2 groups receiving IV medication therefore represent the residual magnitude of reduction at the end of the 2-month or 3-month dosing interval. Serum CTX assays (the Elecsys  $\beta$ -CrossLaps/Serum assay and the Elecsys 2010 system; Roche Diagnostics, Basel, Switzerland) were performed at a central site (Synarc, Lyon, France).

**Tolerability and safety assessments.** Adverse events were continuously monitored, classified by body system and preferred term (using MedDRA version 7.0). Adverse events were considered to be treatment-related if they were reported as being remotely, possibly, or probably related to the study medication.

Physical examinations were performed at the baseline and 12-month visits. Laboratory safety parameters (e.g., hematology and clinical chemistry) were also assessed. Blood samples for laboratory tests were obtained at the screening visit and at 3, 4, 6, 8, 9, and 12 months, just before the scheduled IV dose (active or placebo).

Serum creatinine concentrations were measured at the time of screening, then again at 4, 8, and 12 months in the every-2-months arm and at 3, 6, 9, and 12 months in the every-3-months arm, immediately before the scheduled IV dose (active drug or placebo). Clinically relevant changes in the serum creatinine level were defined as either an increase from baseline of  $\geq 0.5$  mg/dl (if the baseline creatinine level was within normal limits for age [ $< 1.4$  mg/dl]) or  $\geq 1$  mg/dl (if the baseline creatinine level was abnormal [ $\geq 1.4$  mg/dl]), or a 2-fold increase from the baseline value at any time point. Serum creatinine concentrations were also used to estimate creatinine clearance, using the Cockcroft-Gault equation (17).

Clinical vertebral and nonvertebral fractures were monitored from adverse event reporting (all fractures were confirmed radiographically). Flu-like illness, a combination of the investigator-reported terms influenza-like illness and acute-phase reaction, was prospectively identified. All events and events occurring within 3 days of dosing and lasting for  $\leq 7$  days, consistent with the typical characteristics of flu-like illness, were considered.

Electrocardiography (EKG) assessments (12-lead) were performed before and after administration of the study drug, at baseline and 6 months, in a subset of patients from the group receiving medication intravenously every 3 months and from the groups receiving oral medication, in order to assess the potential for QT interval prolongation.

**Statistical analysis. Sample size calculation.** For the primary efficacy parameter (change [%] from baseline in lumbar spine BMD), the hypothesis was that the IV and oral regimens would have the same efficacy (allowing for a maximum margin of difference between them of 1 percentage point). Assuming that the standard deviation for the mean change from baseline in all groups would be 4.5 percentage points, a sample size of 318 evaluable patients in each group receiving IV medication (and an aggregate of 318 patients from the groups receiving medication orally) would be required to show noninferiority of IV treatment at a significance level of 2.5% (1-sided parametric *t*-test) with a statistical power of 80%. To allow for noncompliant patients and a projected withdrawal rate of 20%,  $\sim 1,194$  patients in total needed to be randomly allocated to treatment ( $\sim 398$  patients in each IV-treatment arm and 199 patients in each of the oral-treatment arms).

**Analysis populations.** The safety population comprised all randomized patients who received at least 1 dose of study medication and had at least 1 followup data point (total exclusions = 13 patients). The intent-to-treat (ITT) population comprised all randomized patients who received at least 1 dose of study medication and had at least 1 efficacy data point



(BMD or serum CTX; total exclusions = 37 patients). The per-protocol (PP) population included all patients in the ITT population who had no major protocol violations (e.g., no dose of study medication [n = 9], baseline lumbar spine [L2–L4] BMD T score greater than  $-2.5$  [n = 18], poor compliance with the oral [n = 248] or IV [n = 165] medication, vitamin D deficiency [n = 1], a concomitant disease that was prohibited according to the protocol [n = 7], use of prohibited treatment prior to study [n = 21], lack of efficacy followup information [n = 28], or lack of reliable BMD data [n = 81]; total exclusions = 291 patients).

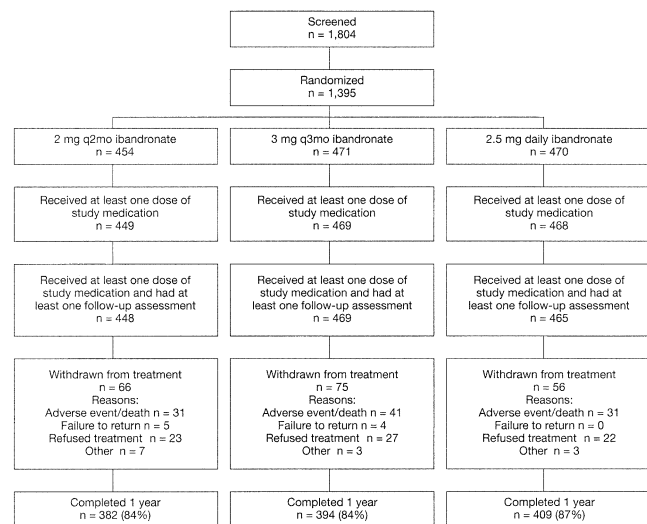
The PP population was the primary analysis population for all efficacy end points. The rationale for this was that a PP population is associated with less variability than is an ITT population (because the latter includes nonconforming patients), and protocol violations are more likely to reduce the treatment effect. For these reasons, analysis of the PP population is considered the more conservative and statistically correct approach for demonstrating noninferiority (18). All analyses performed on the PP population were to be confirmed by ITT analysis.

#### Noninferiority analysis of the primary efficacy variable.

Noninferiority analysis is an established method for demonstrating the therapeutic equivalence of an investigational drug and a reference drug (18). In DIVA, this method was used to compare the change from baseline in lumbar spine BMD (primary end point) in the 2 groups receiving IV medication with that in the 2 groups receiving medication orally. Because the efficacy of oral ibandronate (plus IV placebo every 2 months or every 3 months) was not expected to be influenced by the treatment schedule, it was planned that all efficacy data from the 2 oral-treatment groups would be pooled, provided there were no clinically meaningful differences between baseline data (clinical and demographic) and the efficacy parameters (BMD and serum CTX) at common time points.

In 3 previous studies comparing the effect of oral ibandronate (2.5 mg) and placebo on the percent change from baseline in lumbar spine BMD after 1 year (1,19,20), the smallest difference between the groups was 3.3%. For the noninferiority analysis in the DIVA study, the allowable margin of difference between the groups receiving IV medication and the group (or groups) receiving medication orally was set at 30% of this difference (1 percentage point). Thus, noninferiority of the IV regimens could be concluded if the lower limit of the 2-sided 95% confidence interval (95% CI) (equivalent to a 1-sided 97.5% CI) for the difference between both IV regimens and the oral regimen in the mean change in BMD from baseline was at least  $-1\%$ . The 2 IV-treatment groups were compared sequentially (the every-2-months group first). Only if noninferiority of the IV-treatment groups was demonstrated could the superiority of the IV regimens to the oral regimen be tested using an analysis of variance (ANOVA) model controlling for geographic location and baseline BMD effects (lumbar spine [L2–L4] BMD T score at least  $-3$  or less than  $-3$  and at least  $-3.5$  or less than  $-3.5$ ).

**Analysis of other end points.** The BMD responder rates in each treatment group were compared using a chi-square test, and the absolute and relative changes from baseline in serum CTX levels were summarized. All adverse events and abnormal laboratory test results reported during the first year of the study were included in the safety analysis. The number



**Figure 1.** Patient disposition. “Refused treatment” includes patients who did not cooperate or withdrew consent. “Other” includes insufficient therapeutic response, early improvement, violation of selection criteria at entry, and other protocol violation. q2mo = every 2 months; q3mo = every 3 months.

and proportion (%) of patients in each group who reported adverse events were tabulated for comparison. Because reporting of adverse events and laboratory safety parameters was not expected to be influenced by the treatment schedule, most tolerability and safety data from the 2 groups receiving oral ibandronate were pooled for analysis (except data on compliance and extent of exposure).

## RESULTS

### Patient disposition and baseline characteristics.

Patient disposition is summarized in Figure 1. Of 1,804 women screened, 1,395 were randomly allocated to receive treatment. The sizes of the 3 sample populations were as follows: for ITT, n = 1,358; for PP, n = 1,104; for safety, n = 1,382. Because predefined comparisons of the 2 oral-treatment groups revealed no significant differences between them (data not shown), they were pooled for all efficacy analyses. A subset of 244 patients underwent EKG assessments (157 patients in the every-3-months group and 87 patients in the oral-treatment group).

In the PP population, the group sizes were 355, 368, and 381 for the every-2-months group, the every-3-months group, and the oral-treatment group, respectively. Across all groups, 197 patients withdrew, most commonly because of adverse events. The demographic and clinical characteristics of patients at baseline were well matched across the 3 treatment groups (Table 1).

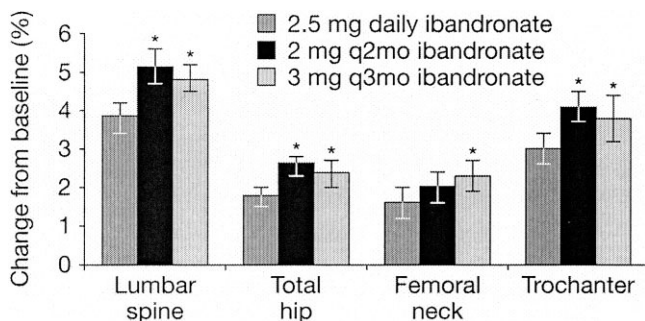
**Table 1.** Characteristics of all patients in the per-protocol population at baseline\*

Characteristic	IV ibandronate, 2 mg every 2 months (n = 355)	IV ibandronate, 3 mg every 3 months (n = 368)	Oral ibandronate, 2.5 mg daily (n = 381)
Age, years	66.6	65.6	65.5
Weight, kg	64.08	63.92	63.41
Height, cm	158.1	158.1	158.4
Body mass index, kg/m <sup>2</sup>	25.648	25.623	25.276
Time since menopause, years	19.3	18.2	18.0
Lumbar spine (L2–L4) BMD, gm/cm <sup>2</sup>	0.747	0.739	0.746
Lumbar spine (L2–L4) BMD, T score	–3.3	–3.3	–3.3
Total hip BMD, gm/cm <sup>2</sup>	0.744	0.733	0.736
Total hip BMD, T score†	–1.909	–1.989	–1.978
Prevalent fracture, %	41.8	43.2	43.7
Serum CTX, median ng/ml	0.50	0.49	0.51
Serum 25(OH)D, ng/ml	25.22	24.33	24.58

\* Except where indicated otherwise, values are the mean. IV = intravenous; BMD = bone mineral density; CTX = C-telopeptide of type I collagen; 25(OH)D = 25-hydroxyvitamin D.  
† NHANES III adjusted.

**Efficacy analysis. Lumbar spine BMD.** At 1 year, similar increases from baseline in lumbar spine BMD were observed in the group receiving IV medication every 2 months (mean 5.1%, 95% CI 4.7, 5.5; n = 353) and the group receiving IV medication every 3 months (mean 4.8%, 95% CI 4.5, 5.2; n = 365). These increases were greater than that in the oral-treatment group (mean 3.8%, 95% CI 3.4, 4.2; n = 377) (Figure 2).

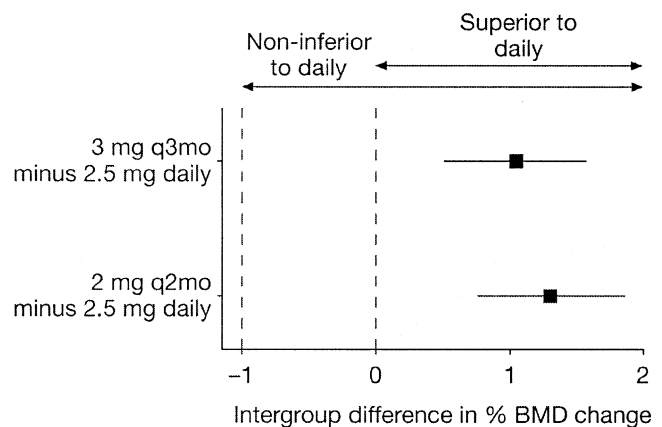
The mean treatment differences (IV minus oral) for change in lumbar spine BMD from baseline were 1.31% (95% CI 0.76, 1.86) for the every-2-months group and 1.03% (95% CI 0.49, 1.58) for the every-3-months group. For both comparisons, the lower 95% confidence limit was above the prespecified margin for noninferiority of –1%, demonstrating that both IV regimens were noninferior to the daily regimen (Figure 3). Subsequent analysis using ANOVA demonstrated that both IV regimens were statistically superior to the oral regimen



**Figure 2.** Mean change from baseline in lumbar spine and proximal femur bone mineral density after 1 year in the per-protocol population. q2mo = every 2 months; q3mo = every 3 months. Bars show the 95% confidence interval. \* =  $P < 0.05$  versus 2.5 mg daily ibandronate.

( $P < 0.001$  for both comparisons). The corresponding analyses performed on the ITT population supported the findings in the PP population (mean treatment difference 1.22% [95% CI 0.69, 1.75] for the every-2-months group and 1.05% (95% CI 0.53, 1.57) for the every-3-months group;  $P < 0.001$  versus oral treatment for both comparisons).

**Proximal femur BMD.** After 1 year, the increases from baseline in BMD of the proximal femur were similar in the group receiving IV ibandronate every 2 months and the group receiving IV ibandronate every 3 months (2.6% and 2.4%, respectively, for total hip; 2.0%



**Figure 3.** Noninferiority analysis of mean change (%) from baseline in lumbar spine (L2–L4) bone mineral density (BMD) after 1 year in the per-protocol population. Squares and horizontal lines show the mean difference (and 95% confidence interval) between each group receiving medication intravenously (IV) and the group receiving medication orally (expressed as IV minus oral). q3mo = every 3 months; q2mo = every 2 months.

**Table 2.** Change (%) from baseline in serum levels of the bone resorption marker CTX in the per-protocol population\*

Month	IV ibandronate, 2 mg every 2 months		IV ibandronate, 3 mg every 3 months		Oral ibandronate, 2.5 mg daily	
	Median (95% CI)	n	Median (95% CI)	n	Median (95% CI)	n
2	-47.1 (-51.0, -43.8)	348	-	-	-45.0 (-48.7, -40.5)	181
3	-	-	-43.2 (-45.9, -40.8)	356	-54.1 (-57.8, -48.7)	192
4	-61.4 (-63.2, -58.4)	349	-	-	-57.6 (-66.7, -50.0)	180
6	-65.1 (-67.4, -62.5)	346	-58.4 (-61.5, -55.2)	353	-62.5 (-65.3, -60.0)	372
12	-64.6 (-67.2, -62.5)	345	-58.6 (-61.5, -55.4)	352	-62.6 (-66.0, -58.9)	368

\* CTX = C-telopeptide of type I collagen; IV = intravenous; 95% CI = 95% confidence interval.

and 2.3%, respectively, for femoral neck; and 4.1% and 3.8%, respectively, for trochanter) (Figure 2). These increases were significantly greater than those in the oral-treatment group (1.8%, 1.6%, and 3.0%, respectively;  $P < 0.05$  for all comparisons except the every-2-months IV regimen versus the oral-treatment regimen at the femoral neck). Again, corresponding analyses in the ITT population supported the findings in the PP population.

*Analysis of responder rates for lumbar spine and total hip BMD.* The proportion of patients in the 2 groups receiving IV medication whose lumbar spine BMD at 1 year was equal to or greater than the baseline value was significantly larger than that in the oral-treatment group; responder rates were 92.6% in the every-2-months group, 92.1% in the every-3-months group, and 84.9% in the oral-treatment group ( $P < 0.01$  for both comparisons). In addition, significantly more patients in the every-2-months group (86.4%) and the every-3-months group (82.3%) achieved a total hip BMD value equal to or greater than the baseline value than did patients in the oral-treatment group (75.1%;  $P < 0.01$  for both comparisons). The proportion of patients for whom values for both lumbar spine and total

hip BMD were equal to or greater than baseline values was also significantly greater in the groups receiving IV treatment (80.9% and 76.2% in the every-2-months and every-3-months groups, respectively) than in the oral-treatment group (67.2%;  $P < 0.01$  for both comparisons). Compared with the oral-treatment arm, larger proportions of patients in the IV-treatment arms responded to treatment with substantial (greater than the least significant change) increases in lumbar spine BMD of  $\geq 6\%$  or total hip BMD of  $\geq 3\%$  (39.4%, 37.8%, and 26.3% for the lumbar spine and 41.9%, 37.8%, and 33.2% for the total hip in the every-2-months, every-3-months, and oral-treatment arms, respectively).

*Serum CTX.* Pronounced decreases from baseline in serum CTX levels were observed in all treatment groups at the first sampling point (either 2 or 3 months after the start of treatment), and levels decreased further over the remainder of the study period (Table 2). After 1 year, the median reduction from baseline in the serum CTX level was similar in the 3 treatment groups (-64.6% [95% CI -67.2, -62.5], -58.6% [95% CI -61.5, -55.4], and -62.6% [95% CI -66.0, -58.9] in the every-2-months, every-3-months, and oral-treatment groups, respectively).

**Table 3.** Proportion of patients in each group who reported adverse events (safety population)\*

	IV ibandronate, 2 mg every 2 months (n = 448)	IV ibandronate, 3 mg every 3 months (n = 469)	Oral ibandronate, 2.5 mg daily (n = 465)
Any AE	365 (81.5)	357 (76.1)	360 (77.4)
Any treatment-related AE	197 (44.0)	183 (39.0)	155 (33.3)
Any treatment-related AE that led to withdrawal	24 (5.4)	31 (6.6)	21 (4.5)
Any SAE	40 (8.9)	35 (7.5)	37 (8.0)
Any treatment-related SAE	4 (0.9)	2 (0.4)	1 (0.2)
Any treatment-related SAE that led to withdrawal	2 (0.4)	0 (0)	0 (0)
Deaths	1 (0.2)	2 (0.4)	1 (0.2)

\* Values are the number (%). Any treatment-related adverse event (AE) or any treatment-related serious AE (SAE) is an event considered by the investigator to be either remotely, possibly, or probably related to the study medication. IV = intravenous.

**Safety assessments. Tolerability (adverse events).** After 1 year, the incidence of (proportion of patients reporting) all adverse events (76–81%), treatment-related adverse events (33–44%), and treatment-related adverse events that led to withdrawal (4.5–6.6%) was similar for the 3 treatment groups (Table 3). The most frequently reported treatment-related adverse events involved the GI and musculoskeletal systems, consisting primarily of dyspepsia (3.4–4.1%), upper abdominal pain (3.0–3.6%), arthralgia (2.4–3.6%), and flu-like illness (0.9–4.1%). No cases of avascular necrosis of the jaw were reported.

Of 112 patients who reported serious adverse events, 7 reported serious adverse events that were considered to be at least remotely related to the study medication, and the incidence of serious adverse events was similar in the 3 groups (Table 3). Four deaths occurred, none of which was considered to be related to the study medication.

**Renal tolerability and safety.** The incidence of renal adverse events was low and similar across the treatment groups (2%, 3%, and 2% in the oral-treatment, every-2-months, and every-3-months groups, respectively). No cases of acute renal failure were reported. Serum creatinine levels were similar in all 3 treatment groups at each time point. There was no change in the mean serum creatinine level from baseline to month 12 in any treatment group. No patient experienced a continuous increase in the serum creatinine concentration during the observation period. Six patients (4 in the every-2-months group and 2 in the every-3-months group) had a clinically relevant change in the serum creatinine level at any 1 time point during the observation period. All of these patients had a normal baseline serum creatinine level (<1.4 mg/dl) and a temporary elevation of  $\geq 0.5$  mg/dl at a single time point. For 1 patient, this represented a 2-fold increase from baseline. Temporary exacerbations of underlying disorders known to compromise kidney function appeared to be the cause in most (5 of 6) of these patients, with none of the observed changes considered to be treatment-related. Baseline creatinine clearance values, which were estimated using the Cockcroft-Gault equation, were <90 ml/minute in 95.0% of patients, and <60 ml/minute in 50.5% of patients. The proportion of patients with any decline in creatinine clearance at any time point was similar between the every-2-months group (14.1%), the every-3-months group (17.3%), and the oral-treatment group (14.1%).

**Clinical fractures.** At 1 year, no differences in the number of clinical fractures were observed between the

groups receiving IV treatment and the oral-treatment group. In total, 43 patients (3.1%) experienced clinical fractures (radiographically confirmed), including non-vertebral fractures: 13 fractures each occurred in the every-2-months group and the every-3-months group, and 17 fractures occurred in the oral-treatment group.

**Flu-like illness.** Although the overall incidence of flu-like illness was low, the incidence was higher in the groups receiving IV treatment than in the oral-treatment group (5.1% and 4.9% in the every-2-months and every-3-months groups, respectively, versus 1.1% in the oral-treatment group). When the typical onset (within 3 days of dosing) and duration ( $\leq 7$  days) of flu-like illness were considered, the incidence of flu-like illness in these 3 groups was 3.8%, 3.6%, and 0.6%, respectively. The specific diagnosis of myalgia was reported for 14 patients (3.1%), 6 patients (1.3%), and 1 patient (0.2%) in the every-2-months, every-3-months, and oral-treatment groups, respectively. In these 3 groups, arthralgia was reported for 5 patients (1.1%), 6 patients (1.3%), and 1 patient (0.2%), respectively. Most events occurred at the time of initial administration only (>80% of affected patients reported no repeat symptoms), were generally mild to moderate in intensity, were transient in nature, and resolved without any treatment. Withdrawal from the trial due to these symptoms was rare (0.4% of patients in the oral-treatment group, 1% of those in the every-2-months group, and 2.6% of patients in the every-3-months group).

**Cardiac safety.** EKG examinations in a subset of 244 patients demonstrated that ibandronate treatment had no measurable effect on heart rate, atrioventricular conduction, cardiac depolarization, the QT interval, or the QT interval corrected for heart rate. In addition, EKG examination identified no differences between the oral and IV regimens. In all treatment groups, cardiac adverse events were infrequent: 5% (n = 24) in the every-2-months group, 3% (n = 15) in the every-3-months group, and 3% (n = 12) in the oral-treatment group.

## DISCUSSION

The DIVA study aimed to demonstrate the non-inferiority of every-2-months and every-3-months regimens of IV ibandronate compared with an approved regimen of daily oral ibandronate that has previously shown significant and substantial antifracture efficacy in postmenopausal women with osteoporosis (3-year vertebral fracture risk reduction, 52%) (1). The results presented in this report show the effects after 1 year of treatment. Both of the IV regimens produced a similar



increase from baseline in lumbar spine BMD (5.1% and 4.8%) that was greater than that provided by the regimen of daily oral ibandronate (3.8%). Prespecified statistical analyses demonstrated the noninferiority of both IV-treatment regimens compared with the oral-treatment regimen. The superiority of both IV-treatment regimens compared with the oral-treatment regimen was also prospectively proven. Results for secondary efficacy parameters consistently supported the results for the primary study end point. Increases from baseline in total hip BMD were similar in the 2 groups receiving IV medication (2.6% and 2.4%), as were the proportions of patients responding to treatment with BMD increases: similar and substantial proportions of patients in the 2 IV-treatment groups achieved lumbar spine and/or total hip BMD readings that were equal to or greater than baseline values.

The degree of reduction in the level of the bone resorption marker serum CTX was similar in all 3 groups in our study, after both 6 and 12 months. This finding is noteworthy, because the magnitude of bone resorption marker reduction observed in the 2 groups receiving IV medication compares favorably with that noted at 3 years in the BONE study (1). In that study, 3 years of treatment with 2.5 mg of oral ibandronate daily produced a 52% reduction in the risk of vertebral fractures and a 6.5% increase in lumbar spine BMD (1). These effects were accompanied by a reduction in the level of bone resorption markers (as assessed by the urinary concentration of CTX corrected for creatinine) of 65.3% at 3 years (2). In previous studies of IV ibandronate that used lower doses (0.5 mg and 1 mg every 3 months) than those used in the DIVA study, the reduction in bone turnover was only modest (7.3% and 10.8%, respectively, versus placebo), leading to suboptimal increases in lumbar spine BMD of 3.9% and 4.9%, respectively, after 3 years and an insignificant reduction in the risk of vertebral fracture (21). However, the dose dependency of these effects was demonstrated by the Intermittent Regimen Intravenous Ibandronate Study, in which a larger IV dose given with the same dose-free interval (2 mg every 3 months) for just 1 year produced significantly greater lumbar spine (L1–L4) BMD increases and decreases in the level of urinary CTX/creatinine than those observed with the regimen in which 1 mg was administered every 3 months (15).

At the currently studied doses, IV ibandronate injections were well tolerated, with safety and tolerability profiles similar to those for daily oral ibandronate, with no renal tolerability concerns as have been observed with other IV bisphosphonates (22–25). These

results are consistent with those previously reported for IV ibandronate injections (14,15,21,26,27). The incidence of flu-like illness was, as expected, higher in the groups receiving IV medication than in the group receiving oral medication. Nevertheless, the absolute incidence of this event, as well as the incidence of myalgia and arthralgia, was low (1.1–5.1% in the IV-treatment groups and 0.2–0.6% in the oral-treatment group). Symptoms mostly occurred at the time of the first IV injection (>80% of affected patients reported no repeat symptoms) and were generally mild to moderate in intensity and transient in nature.

The findings of the DIVA study indicate that IV ibandronate injections administered every 2 months or every 3 months are at least as effective and similarly well tolerated as an established regimen of daily oral ibandronate, in postmenopausal women with osteoporosis. Intravenous administration of ibandronate is likely to be advantageous for patients who cannot tolerate oral bisphosphonates or have difficulty complying with oral treatment.

#### ACKNOWLEDGMENTS

We are indebted to all those who contributed to the conduct and analysis of the DIVA study, including Peter Alexandersen, Claude Laurent Benhamou, Gerolamo Bianchi, Edward Czerwinski, Kurt Datz, Tobie de Villiers, Jan de Weerd, Richard Dumas, John Eisman, Graham Ellis, Ronald Emkey, James Engelbrecht, Pedro Garcia, Johan Halse, Hans Christian Hoeck, Michael Hooper, Lars Hyldstrup, Robert Josse, Howard Knapp, Richard Kremer, Hans-Peter Kruse, Bente Langdahl, Michael Lewiecki, Michael Lillestol, Krzysztof Lipinski, Barry Lubin, Jesus Gonzalez Macias, Emilio Martin Mola, Xavier Nogues, Ranuccio Nuti, W. P. Olszynski, Guillermo Ortiz, Johannes Pfeilschifter, B Pernel, Richard Prince, Chris Recknor, Sherwyn Schwartz, Ego Seeman, Louis-George Ste-Marie, Jan Stepan, Istvan Szombati, Antonio Torrijos, Vaclav Vyskocil, Robert Weinstein, and Mone Zaidi. We also thank Scott Malkin (medical writer) for assisting with the development of this manuscript.

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