

# Two-year efficacy and tolerability of intermittent intravenous ibandronate injections in postmenopausal osteoporosis: the DIVA study

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## ABSTRACT

**Purpose.** In some patient groups, oral bisphosphonates may be unsuitable for use or even contraindicated. An efficacious and well-tolerated intravenous (i.v.) bisphosphonate could therefore be of significant utility. In the DIVA study, 2mg every 2 months (q2mo) or 3mg every 3 months (q3mo) i.v. ibandronate injections provided superior efficacy ( $p < 0.001$ ) at the lumbar spine to an established daily oral ibandronate regimen (2.5mg) at 1 year in women with postmenopausal osteoporosis. All regimens were well-tolerated. Here, we report the 2-year outcomes.

**Methods.** All participants in this double-blind, double-dummy, phase III, non-inferiority study were women (aged 55–80 years;  $\geq 5$  years since menopause) with postmenopausal osteoporosis (lumbar spine [L2–L4] bone mineral density [BMD] T-score  $< -2.5$ ). Participants received i.v. or oral treatment plus placebo to maintain blinding. Daily calcium (500mg) and vitamin D (400IU) supplements were taken. At 2 years, efficacy endpoints included relative change in lumbar spine and hip BMD and serum CTX. Adverse events were continuously monitored.

**Results.** A total of 1,395 women were randomized. At 2 years, increases in lumbar spine BMD were obtained in all treatment arms: 6.4% in the q2mo arm ( $n=320$ ), 6.3% in the q3mo arm ( $n=334$ ) and 4.8% in the daily arm ( $n=334$ ). As at 1 year, both i.v. regimens were proven non-inferior (margin at year 2: 1.3%) and also superior ( $p < 0.001$ ) to the oral regimen. At all hip sites, increases in BMD were also observed (Table), with consistently greater gains in the i.v. arms than in the oral arm. Correspondingly, serum CTX concentrations were also substantially reduced (median reduction: 53.4–59.9%). At 2 years, the good tolerability observed at 1 year was again seen with both i.v. regimens. A similar incidence of adverse events (85.3–88.6%) and adverse events leading to withdrawal (9.8–11.7%) was observed between the daily oral and the i.v. arms.

**Conclusions.** Intermittent i.v. ibandronate injections are an efficacious and well-tolerated treatment option for patients with postmenopausal osteoporosis, and may be useful for those who are unsuitable or contraindicated for oral bisphosphonate administration. The additional BMD increases provided by the i.v. regimens compared with the oral regimen with proven antifracture efficacy may provide further antifracture benefits.

**Table. Percentage change (mean, SD) from baseline in lumbar spine and hip BMD at 2 years (per-protocol [PP] population).**

	2.5mg daily oral IBN (n=330)	2mg q2mo i.v. IBN (n=316)	3mg q3mo i.v. IBN (n=333)
Lumbar spine*	4.8 (4.9)	6.4 (4.7)	6.3 (5.0)
Total hip	2.2 (3.7)	3.4 (3.0)	3.1 (4.5)
Femoral neck	2.2 (4.3)	2.7 (4.2)	2.8 (4.7)
Hip trochanter	3.5 (4.7)	5.0 (4.5)	4.9 (7.5)

\* $n=334$ , 320 and 334, respectively

## INTRODUCTION

- Oral bisphosphonates may be contraindicated for patients who experience gastrointestinal intolerance or are unable to comply with the strict dosing guidelines. An efficacious and well-tolerated i.v. bisphosphonate would provide them with a useful alternative.
- The DIVA study compares the efficacy and safety of i.v. ibandronate injections, 2mg q2mo and 3mg q3mo with a proven daily oral ibandronate regimen (2.5mg; 3-year vertebral fracture risk reduction: 52%) in women with postmenopausal osteoporosis.<sup>1</sup>
- At 1 year, both i.v. ibandronate regimens provided superior efficacy ( $p < 0.001$ ) at the lumbar spine to the established daily oral ibandronate regimen, and all regimens were well tolerated.<sup>2</sup>
- Here we report the 2-year outcomes.

## METHODS

### Study design

- Randomized, double-blind, double-dummy, phase III, non-inferiority study.
- Women (aged 55–80 years;  $\geq 5$  years since menopause) with postmenopausal osteoporosis (mean lumbar spine [L2–L4] BMD T-score  $< -2.5$  and  $\geq -5.0$ ), randomized for 2 years into one of four treatment groups in a 2:1:2:1 ratio, respectively
  - 2mg q2mo i.v. ibandronate injection plus daily oral placebo (2)
  - 2.5mg daily oral ibandronate plus q2mo i.v. placebo injection (1)
  - 3mg q3mo i.v. ibandronate injection plus daily oral placebo (2)
  - 2.5mg daily oral ibandronate plus q3mo i.v. placebo injection (1).

- Patients received daily oral calcium (500mg) and vitamin D (400IU).

### Study endpoints

- The primary efficacy endpoint was the mean percent change from baseline in lumbar spine (L2–L4) BMD after 1 year.
- Secondary efficacy endpoints included
  - the mean percent change from baseline in lumbar spine (L2–L4) BMD after 2 years and in proximal femur (total hip, trochanter and femoral neck) BMD after 1 and 2 years
  - the proportion of participants defined as responders after 1 and 2 years, i.e. achieving
    - lumbar spine BMD increases above baseline
    - total hip BMD increases above baseline
    - lumbar spine and total hip BMD increases above baseline
  - median percent change from baseline in serum CTX, measured at baseline, 2, 4, 6, 12 and 24 months in the q2mo arm and baseline, 3, 6 and 12 and 24 months in the q3mo arm.
- Adverse events, including influenza-like illness, renal safety and clinical fractures, were continuously monitored.

### Statistical analysis

- Changes in lumbar spine BMD with the i.v. and oral regimens were compared after 2 years using a non-inferiority analysis to establish therapeutic equivalence
  - to preserve at least 70% of the daily regimen's effect, the non-inferiority margin for DIVA was set at 30% of this difference, i.e. 1.3%
  - therefore, demonstration of equivalent efficacy requires that the lower boundary of the one-sided 97.5% CI for the difference after 2 years in mean percent change from baseline in lumbar spine BMD be  $\geq -1.3\%$ .

- Should non-inferiority be demonstrated, then a prospectively specified test of the superiority of the i.v. regimens to the oral regimen would be undertaken (ANOVA).

### Analysis populations

- The most conservative way to demonstrate non-inferiority is to use the PP population; this was therefore the primary analysis population for all efficacy endpoints.
- Intent-to-treat (ITT) analyses were also performed for all efficacy endpoints.

## RESULTS

### Patient characteristics

- A total of 1,395 women were randomized. Table 1 shows patient demography.
- Of these, 1,089, 1,358, and 1,382 fulfilled criteria for the PP, ITT, and safety 2-year analyses, respectively.
- The treatment arms were well balanced for baseline characteristics.

**Table 1. Baseline demographics (mean; safety population).**

	2.5mg daily IBN (n=465)	2mg q2mo IBN (n=448)	3mg q3mo IBN (n=469)
Age (years)	65.7	66.6	65.8
Weight (kg)	63.57	64.33	64.02
Height (cm)	158.3	158.0	158.1
BMI (kg/cm <sup>2</sup> )	25.4	25.8	25.7
Time since menopause (years)	18.1	19.3	18.6
Lumbar spine (L2–L4) BMD (g/cm <sup>2</sup> )	0.747	0.747	0.745
Lumbar spine (L2–L4) BMD (T-score)	-3.26	-3.27	-3.27
Total hip BMD (g/cm <sup>2</sup> )	0.734	0.744	0.738
Total hip BMD (T-score)*	-2.00	-1.90	-1.96
Prevalent fracture (%)	43.5	42.1	43.9
Serum CTX (ng/mL)	0.553	0.525	0.525
25-OH-D (ng/mL)	24.50	25.22	24.31

\*NHANES III adjusted

### Efficacy analysis

#### Lumbar spine BMD

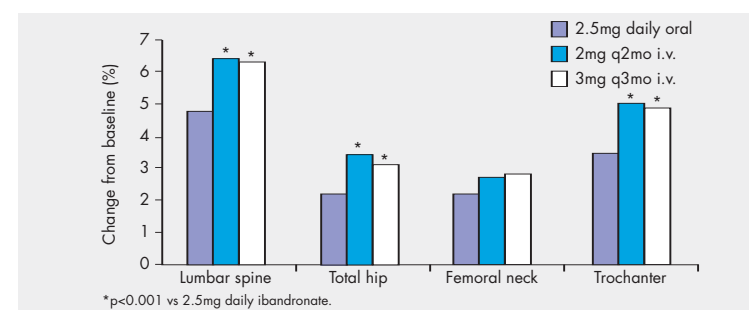
- Sizeable gains in lumbar spine BMD were achieved in all treatment arms at 2 years (Figure 1).
- As at 1 year, both i.v. regimens were
  - proven non-inferior to the oral regimen (Figure 2)
  - prospectively demonstrated to be superior to the oral regimen ( $p < 0.001$ ).
- The ITT analysis yielded similar results.

#### Proximal femur BMD

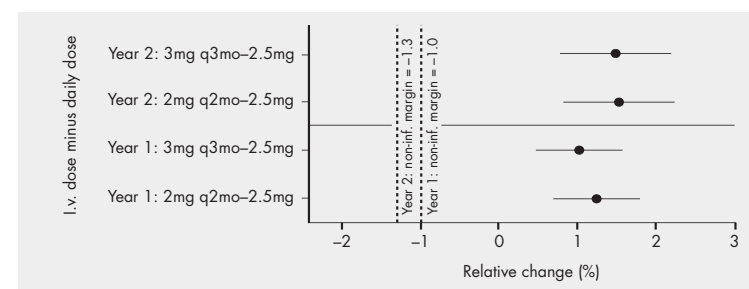
- Sizeable gains in proximal femur BMD were attained in all treatment arms at 2 years (Figure 1).
- Consistently greater BMD increases were noted in the i.v. arms than in the oral arm at all hip sites.
- The ITT analysis yielded similar results.

#### Lumbar spine and total hip responder analysis

- A greater proportion of patients in the i.v. arms than the oral arm attained lumbar spine and/or total hip increases above baseline ( $p \leq 0.004$  for all comparisons). Data confirmed findings from year 1 of the study.<sup>2</sup>



**Figure 1. Mean (95% CI) percent change in lumbar spine and proximal femur BMD after 2 years (PP).**



**Figure 2. Graphical representation of the non-inferiority analysis of mean percent change from baseline in lumbar spine (L2–L4) BMD after 1 and 2 years (PP).**

#### Serum CTX

- Marked reductions in serum CTX were seen in both i.v. treatment arms at the first assessment (Table 2).
- At the first parallel assessment (6 months) and at all subsequent assessments, serum CTX reductions were substantial, remaining at 50% or more below baseline values and well within the premenopausal ranges (sCTX  $\leq 0.536$  ng/mL) (Table 2), even though sampling in the i.v. arms was performed at the end of the 2- or 3-month dosing interval.

**Table 2. Median change (%; n) from baseline in sCTX (PP population).**

Months	2.5mg daily oral IBN	2mg q2mo i.v. IBN	3mg q3mo i.v. IBN
2	-45.0 (173)	-47.9 (340)	-
3	-54.1 (189)	-	-43.3 (349)
4	-58.7 (170)	-61.4 (343)	-
6	-63.4 (358)	-65.3 (342)	-58.1 (345)
12	-63.5 (360)	-64.7 (342)	-59.0 (347)
24	-59.9 (310)	-55.6 (301)	-53.4 (298)

### Safety

#### Overall

- At 2 years, the favorable tolerability observed at 1 year was again seen with both i.v. regimens.
- A similar incidence of adverse events and adverse events leading to withdrawal was observed in the daily oral and i.v. arms (Table 3).

#### Flu-like illness

- The incidence of possibly or probably related flu-like illness was low although somewhat higher in the two i.v. arms than in the oral arm (4.7%, 4.5% and 0.9% in the 2mg q2mo, 3mg q3mo and daily arms, respectively).
- Only a small number of events were reported during the second year of the study as most occurred only with the first injection. Symptoms were transitory, usually lasting only 1–2 days.
- Only five patients, four in the 3mg q3mo arm and one in the 2mg q2mo, withdrew as a result of this related event.

#### Renal safety

- Over the entire 2-year treatment period, the proportion of patients with adverse events attributable to the renal and urinary disorders was low and similar in all three treatment groups ( $< 5\%$ ).
- Changes in serum creatinine values and estimated creatinine clearance versus baseline were similar between treatment groups. Furthermore, the estimated annual rate of decline of creatinine clearance in each dose group is consistent with age-related decline (approximately 1 mL/min per year).

#### Clinical osteoporotic fractures

- After 2 years, the incidence of clinical osteoporotic fractures was similar in i.v. treated patients (5.8% in both i.v. arms) and oral daily patients (6.9%).

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

	2.5mg daily IBN (n=465)	2mg q2mo IBN (n=448)	3mg q3mo IBN (n=469)
Any adverse event	87.7	88.6	85.3
Any drug-related adverse event	36.8	46.4	42.0
Any drug-related adverse event leading to withdrawal	6.0	6.5	7.7
Any serious adverse event	14.4	16.3	13.2
Any drug-related serious adverse event	0.9	1.1	0.4
Any drug-related serious adverse event leading to withdrawal	0.4	0.7	0
Death, n (%)	4 (<1)	3 (<1)	2 (<1)

## CONCLUSIONS

- The 2-year findings from the DIVA study demonstrate that both i.v. ibandronate injections were more effective, as determined by BMD gains, than the proven oral daily regimen.
- In particular, the 3mg q3mo regimen offers the convenience of a quarterly injection, which can be timed to coincide with clinic visits, whilst providing superior efficacy and a similar safety profile when compared with the other dosing regimens.
- I.v. administration of ibandronate may offer an effective, alternative treatment option for patients who cannot tolerate oral bisphosphonates or cannot comply with the strict dosing guidelines.

## REFERENCES

- Chesnut CH, et al. J Bone Miner Res 2004;19:1241–9.
- Delmas PD, et al. Arthritis Rheum 2006. In submission.