

# Consistent efficacy with intermittent intravenous ibandronate injections in postmenopausal osteoporosis: DIVA 2-year analysis

Stepan JJ,<sup>1</sup> Bianchi G,<sup>2</sup> Czerwinski E,<sup>3</sup> Hughes C,<sup>4</sup> Mairon N,<sup>4</sup> Masanauskaitė D,<sup>4</sup> Stakkestad JA<sup>5</sup>

<sup>1</sup>Charles University, Prague, Czech Republic; <sup>2</sup>Ospedale La Colletta, Azienda Sanitaria Genovese, Genova, Italy; <sup>3</sup>Krakow Medical Centre, Krakow, Poland; <sup>4</sup>F. Hoffmann-La Roche Ltd, Basel, Switzerland; <sup>5</sup>CECOR AS, Haugesund, Norway

## SUMMARY

- Postmenopausal osteoporosis is a chronic condition that affects a diverse population of women.
- With osteoporosis treatments, these divergent patient characteristics may influence treatment outcomes.
- In the Dosing IntraVenous Administration (DIVA) study, 2mg every 2 months (q2mo) and 3mg every 3 months (q3mo) intravenous (i.v.) ibandronate (Bonviva®) injections were at least as effective (with regard to bone mineral density [BMD] increases by non-inferiority test) at 1 and 2 years as an established daily oral ibandronate regimen (2.5mg) in women with postmenopausal osteoporosis.
- A prespecified analysis explored the influence of several patient characteristics on treatment outcomes. Data from the clinically relevant baseline characteristics, lumbar spine BMD T-score, fracture history and age, are presented here.
- At 1 and 2 years, substantial and generally similar gains in lumbar spine BMD were observed in all patient subgroups, regardless of the dosing regimen.
- In all subgroups analysed, gains in lumbar spine BMD in the i.v. arms were non-inferior to those in the daily arm, as observed in the overall population.
- Ibandronate i.v. injections have a consistent effect on BMD, regardless of baseline patient characteristics.

## INTRODUCTION

- Osteoporosis affects a heterogeneous population of postmenopausal women.
- In osteoporosis management, treatment outcomes may be influenced by the often subtle variation in characteristics observed among patients.
- Ibandronate is a potent, nitrogen-containing bisphosphonate that provides antifracture efficacy in postmenopausal osteoporosis when administered continuously or with extended dosing intervals.<sup>1</sup>
- In the DIVA study, the efficacy of two novel intermittent i.v. ibandronate injection regimens (2mg q2mo and 3mg q3mo) was compared with an efficacious daily oral ibandronate regimen (2.5mg; 3-year vertebral fracture risk reduction: 62%)<sup>1</sup> in women with postmenopausal osteoporosis.<sup>2,3</sup>
- On the basis of these findings, quarterly i.v. ibandronate injections (3mg) have recently been approved in the EU.
- Prospective analyses of DIVA assessed the influence of patient characteristics on the treatment outcomes of ibandronate in the overall patient population and patient subgroups. Data for clinically relevant baseline characteristics are presented here.

## METHODS

### Study design and participants

- Randomised, double-blind, double-dummy, phase III, non-inferiority study.
- Women (aged 55–80 years; ≥5 years since menopause [YSM]) with osteoporosis (lumbar spine [L2–L4] BMD T-score <−2.5 and ≥−5.0).
- Participants were randomised in a 2:1:2:1 ratio to calcium (500mg/day) and vitamin D (400IU/day) supplements plus either
  - 2mg q2mo i.v. ibandronate injections and daily oral placebo (2)
  - 2.5mg daily oral ibandronate and q2mo i.v. placebo injections (1)
  - 3mg q3mo i.v. ibandronate injections and daily oral placebo (2)

– 2.5mg daily oral ibandronate and q3mo i.v. placebo injections (1).

- Oral medication was taken with plain water after an overnight fast (≥6 hours); patients were instructed to stay upright and continue fasting for at least 1 hour after dosing.

### Efficacy analyses

- The primary efficacy analysis was change (%) in lumbar spine BMD from baseline at 1 year; a confirmatory analysis was also performed at 2 years.
- Exploratory analyses were performed using prospectively defined patient subgroups at 1 year<sup>4</sup> and at 2 years. The following subgroup analyses at 2 years are presented here
  - baseline lumbar spine BMD T-score: <−2.5 to ≥−3.0; <−3.0 to ≥−3.5; <−3.5 to ≥−5.0
  - fracture history since the age of 45 years: presence or absence
  - age: <70 years or ≥70 years.

### Statistical analysis

- In the overall population, changes (%) in lumbar spine BMD with the i.v. and oral regimens were compared at 2 years by non-inferiority test (margin: 1.3%).<sup>3</sup>
- If non-inferiority of the i.v. regimens was demonstrated, superiority versus the oral regimen was tested using an analysis of variance (ANOVA) model.
- No formal non-inferiority margins were set for the patient subgroups. However, treatment effects versus the daily regimen were evaluated using 95% CI, and compared with the overall non-inferiority margin of 1.3%.
- All analyses were performed in the per-protocol (PP) population.

## RESULTS

### Patient characteristics

- In total, 1,395 women were randomised into the study.
- Of these women, 1,089 fulfilled the criteria for inclusion in the PP population at year 2.
- Patient characteristics were well balanced across treatment groups at baseline, with the exception of a statistically significant ( $p < 0.05$ ) difference in age between patients in the oral and 2mg q2mo i.v. arms (Table 1).
- Each patient subgroup comprised at least 20% of the total study population (Table 2).

Table 1. Patient baseline characteristics (mean; PP population; 2-year analysis).

Characteristic	2.5mg daily oral IBN (n=375)	2mg q2mo i.v. IBN (n=350)	3mg q3mo i.v. IBN (n=364)
Age (years)	65.6	66.5	65.6
Weight (kg)	63.5	64.1	64.0
Height (cm)	158.4	157.9	158.1
YSM	18.1	19.2	18.2*
Lumbar spine (L2–L4) BMD (T-score)	−3.255	−3.279	−3.285*
Prevalent fracture (%)	44.4	41.8	42.9
Serum CTX (ng/mL)	0.510 <sup>†</sup>	0.490 <sup>‡</sup>	0.490 <sup>†</sup>

\*n=363; <sup>†</sup>n=369; <sup>‡</sup>n=350; <sup>§</sup>n=358

### Lumbar spine BMD gains: overall population

- At 2 years, substantial increases in lumbar spine BMD were obtained in all treatment arms (Table 2), as at year 1.
- Increases in the i.v. arms were consistently greater than those in the oral arm.
- Both i.v. regimens were proven non-inferior and superior ( $p < 0.001$ ) to the oral regimen.

Table 2. Mean change (%; n) from baseline in lumbar spine (L2–L4) BMD by subgroup (mean; PP population; 2-year analysis).

	2.5mg daily oral IBN	2mg q2mo i.v. IBN	3mg q3mo i.v. IBN
Overall population	4.8 (334)	6.4 (320)	6.3 (334)
Baseline BMD <−2.5 to ≥−3.0	4.9 (127)	5.9 (125)	5.2 (130)
Baseline BMD <−3.0 to ≥−3.5	4.4 (105)	6.1 (95)	6.3 (109)
Baseline BMD <−3.5 to ≥−5.0	5.2 (102)	7.3 (100)	7.8 (95)
No previous fracture*	4.6 (219)	6.5 (210)	6.0 (216)
Previous fracture*	5.2 (115)	6.1 (110)	6.7 (118)
Age <70 years	4.8 (244)	6.1 (205)	6.1 (234)
Age ≥70 years	4.9 (90)	7.0 (115)	6.8 (100)

\*Since age 45

### Lumbar spine BMD gains: subgroup analyses

- At 2 years, sizeable gains in lumbar spine BMD were observed in all patient subgroups, independent of dosing regimen (Table 2).
- Increases in BMD were generally similar across the patient subgroups and between the i.v. regimens (Table 2).
- Versus the oral arm, consistently greater gains in lumbar spine BMD were obtained in all patient subgroups with the i.v. regimens.
- For each subgroup analysed, gains in lumbar spine BMD in the i.v. treatment arms were non-inferior to those observed in the daily arm using a margin of 1.3% (Figure 1).

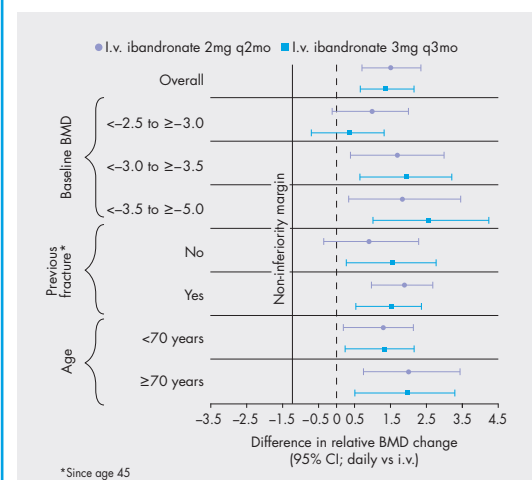


Figure 1. Summary of the difference in means between the 2.5mg daily and the respective i.v. regimens for change (%) and 95% CI from baseline in lumbar spine (L2–L4) BMD in selected subgroups at 2 years (PP population).

## CONCLUSIONS

- In all study subgroups, i.v. ibandronate injections provided sizeable and comparable gains in lumbar spine BMD, which are at least as large as those observed with the daily oral regimen.
- I.v. ibandronate injections have a consistent effect on BMD, regardless of selected baseline patient characteristics.

## REFERENCES

- Chesnut CH, et al. J Bone Miner Res 2004;19:1241–9.
- Delmas PD, et al. Arthritis Rheum 2006. In press.
- Emkey R, et al. Arthritis Rheum 2005;52:4060 (Abstract L8).
- Emkey R, et al. J Bone Miner Res 2005;20(Suppl. 1):S285 (Abstract SU413).

This research was supported by F. Hoffmann-La Roche Ltd and GlaxoSmithKline