

# Intermittent intravenous ibandronate injections are associated with newly formed bone of normal quality: the DIVA study

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## ABSTRACT

**Purpose.** The 2.5mg daily oral ibandronate (Boniva®) regimen has been shown to normalize bone turnover with no adverse effects on the quality of newly formed bone.<sup>1</sup> In the Dosing IntraVenous Administration (DIVA) study, intravenous (i.v.) ibandronate injections (2mg every 2 months [q2mo] and 3mg every 3 months [q3mo]), provided superior efficacy (p<0.001) to an established daily oral ibandronate regimen (2.5mg) for lumbar spine bone mineral density (BMD) increases in postmenopausal women with osteoporosis.<sup>2,3</sup> Here, the effect of i.v. ibandronate on bone safety and remodeling is reported.

**Methods.** A total of 109 patients underwent single bone biopsy after 22 or 23 months of treatment, and qualitative histology and quantitative histomorphometry were assessed in 89 evaluable biopsy cores.

**Results.** In all patients, newly formed bone was of normal lamellar structure with no evidence of marrow fibrosis, cellular toxicity or mineralization defects (as shown by the absence of an excessive amount of osteoid and presence of a normal mineral apposition rate [MAR]; **Table**).<sup>4</sup> In all three groups of ibandronate-treated patients, median activation frequency (Ac.f) was comparable with the levels seen in premenopausal women (0.13/year<sup>2</sup>) and mineralizing surface (MS) was comparable with normal levels seen in healthy postmenopausal women (**Table**).<sup>4</sup> With all three ibandronate regimens, effects were similar and comparable with those obtained previously with daily oral ibandronate.<sup>1</sup>

**Conclusions.** Daily oral and intermittent i.v. ibandronate have similar bone safety profiles in postmenopausal osteoporosis. Bone remodeling was reduced to the healthy premenopausal range and there was no evidence of adverse effects detected on bone mineralization.

**Table. Key histomorphometric parameters (median [90% CI]).**

	2.5mg daily oral (n=32)	2mg q2mo i.v. (n=27)	3mg q3mo i.v. (n=30)	
Osteoid thickness (µm)	5.00 (4.80, 5.70)	4.70 (4.40, 5.20)	5.05 (4.70, 5.90)	
MAR (µm/day)*	0.63 (0.55, 0.64)	0.56 (0.49, 0.61)	0.60 (0.54, 0.66)	
Ac.f* (no. per year)	0.13 (0.08, 0.23)	0.06 (0.03, 0.11)	0.06 (0.05, 0.14)	
MS (%)	1.64 (0.82, 2.94)	0.61 (0.39, 1.29)	0.87 (0.60, 1.89)	
Bone formation rate* (mm <sup>2</sup> /mm <sup>2</sup> /year)	0.05 (0.04, 0.10)	0.02 (0.01, 0.04)	0.04 (0.02, 0.08)	

\*n=29, 22 and 27 for the 2.5mg daily, 2mg q2mo and 3mg q3mo groups, respectively

## INTRODUCTION

- Histomorphometry is a powerful tool for evaluating the effects of therapeutics on bone quality and the bone remodeling process at the tissue level.
- In the oral ibandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) of daily (2.5mg) and intermittent (20mg every other day for 12 doses q3mo; dosing interval >2 months) oral ibandronate, a nitrogen-containing bisphosphonate for postmenopausal osteoporosis, analyses of single bone biopsy samples taken at 3 years demonstrated that newly formed bone was of normal quality and structure; moreover, no adverse effects on mineralization were detected.<sup>1,6</sup>
- The subsequent DIVA study, a randomized, double-blind, double-dummy, phase III, non-inferiority study, demonstrated the superior efficacy of 2mg q2mo and 3mg q3mo i.v. ibandronate injections versus the 2.5mg daily oral ibandronate regimen; qualitative histological and quantitative histomorphometric analyses were also performed at 22 or 23 months to establish the bone safety profile of the investigational regimens and provide further insights into their impact on the bone remodeling process.<sup>2,3</sup>

- The outcome of this analysis, which provides safety information on the highest annual cumulative exposure to ibandronate examined to date (12mg), is reported herein.

## METHODS

### Bone biopsy study design and patient population

- All participants were postmenopausal women (aged 55–80 years, ≥5 years since menopause [YSM]) with osteoporosis (lumbar spine [L2–L4] BMD T-score <−2.5) who received 2 years' treatment with daily calcium (500mg) and vitamin D (400IU), plus either 2mg q2mo i.v. ibandronate injections (plus daily oral placebo), 3mg q3mo i.v. ibandronate injections (plus daily oral placebo) or 2.5mg daily oral ibandronate (plus q2mo or q3mo i.v. placebo injections); written informed consent was provided by all those entering the biopsy study.
- Single transiliac bone biopsies were taken after 22 months (q3mo arms) or 23 months (q2mo arms) of oral or i.v. treatment; prior to biopsy, double tetracycline labeling was performed in the following schedule: 3 days of tetracycline (label 1), 14 days without tetracycline, 3 days of tetracycline (label 2); biopsies were performed 5–14 days after the end of label 2.

- All biopsy samples were analysed centrally (Osteoporosis Research Center, Creighton University, Omaha, Nebraska, USA).

### Analyses

- A qualitative histological analysis was performed to detect the presence of woven bone, marrow fibrosis, mineralization defects and cellular toxicity.
- Quantitative histomorphometric analyses included both static (e.g. osteoid thickness [O.Th], osteoid volume [OV/BV], trabecular thickness [Tb.Th], trabecular number [Tb.N] and trabecular separation [Tb.Sp]) and dynamic (e.g. MAR, Ac.F, MS/BS and bone formation rate [BFR/BV]) parameters.
- Median values and 90% CIs were calculated for all quantitative parameters; data were also compared with normal (reference) data from a patient population consisting of 34 healthy postmenopausal women (aged 45–75 years, ≥1 YSM).<sup>4,5</sup>

## RESULTS

### Study population and patient characteristics

- A total of 109 participants underwent a single transiliac bone biopsy.
- Qualitative histological analysis was performed on all biopsy cores.
- Quantitative histomorphometric parameters were evaluable in 89 samples: 32 in the daily arm, 27 in the q2mo arm and 30 in the q3mo arm; static parameters were evaluable in all samples and both static and dynamic parameters in 77 samples (label was not detected in 12 samples during routine histomorphometry; samples were from all three treatment groups).
- Baseline characteristics of the participants providing evaluable samples were well balanced across the treatment arms (**Table 1**).

### Qualitative histological analysis

- In the i.v. and oral treatment groups, newly formed bone retained its lamellar structure, without signs of woven bone.
- No marrow fibrosis, signs of cellular toxicity or indicators of osteomalacia, such as excessive osteoid, were found.

### Quantitative histomorphometric analysis

#### Bone mineralization

- In all treatment arms, no impairment of mineralization of newly formed bone was detected with active treatment
  - median O.Th values were generally comparable across the i.v. and oral treatment arms and lower than the healthy postmenopausal reference value, as anticipated (**Table 2**); a similar outcome was observed for OV/BV (**Table 2**)

- median MAR values were comparable in all treatment arms and also comparable to the healthy postmenopausal reference value, as expected (**Table 2**).

**Table 1. Baseline patient characteristics of participants providing evaluable samples (mean, SD).**

	2.5mg daily oral (n=32)	2mg q2mo i.v. (n=27)	3mg q3mo i.v. (n=30)	
Age (years)	62.9 (6.70)	65.3 (6.71)	63.4 (6.79)	
Weight (kg)	64.5 (9.55)	68.3 (11.44)	65.7 (10.63)	
Height (cm)	159.4 (6.41)	157.5 (4.92)	161.0 (6.68)	
YSM (years)	15.8 (9.43)	18.7 (10.04)	17.1 (7.48)	
Fracture history (n, %)				
Yes	12 (37.5)	13 (50.0)	15 (50.0)	
No	20 (62.5)	13 (50.0)	15 (50.0)	

#### Bone turnover

- As expected, parameters of bone turnover were comparable in all treatment arms
  - median Ac.F values were generally similar in all active treatment groups (**Table 2**), yet lower than reference values observed in untreated osteoporotic (0.42/year)<sup>6</sup> and healthy (**Table 2**) postmenopausal women; importantly, values were similar to the reference value seen in healthy premenopausal women (0.13/year)<sup>6</sup>
  - median values for MS/BS were broadly similar across the active treatment groups (**Table 2**), but were markedly lower than the healthy postmenopausal reference value, as anticipated (**Table 2**); again, results were not markedly different to that seen in healthy premenopausal women<sup>6</sup>
  - as expected, median values for BFR/BV tended to be lower than the healthy premenopausal reference value (**Table 2**).

#### Bone micro-architecture

- Normal bone micro-architecture was observed in all treatment arms
  - median values for Tb.Th were comparable to the healthy postmenopausal reference value (**Table 2**)
  - compared with healthy postmenopausal reference values, Tb.N was lower and Tb.Sp higher in the active treatment groups, as anticipated (**Table 2**).

**Table 2. Summary of key histomorphometric parameters (median, 90% CI) in DIVA plus normal reference values (healthy postmenopausal women).**

	2.5mg daily oral (n=32)	2mg q2mo i.v. (n=27)	3mg q3mo i.v. (n=30)	Reference values (n=34) <sup>5,6</sup>
Mineralisation				
O.Th (µm)	5.00 (4.80, 5.70)	4.70 (4.40, 5.20)	5.05 (4.70, 5.90)	9.58
OV/BV (%)	0.61 (0.40, 0.91)	0.40 (0.22, 0.70)	0.45 (0.28, 0.59)	1.78
MAR (µm/day)	0.63 (0.55, 0.64)	0.56 (0.49, 0.61)	0.60 (0.54, 0.66)	0.53
Bone turnover				
Ac.f (no./year)	0.13 (0.08, 0.23)	0.06 (0.03, 0.11)	0.06 (0.05, 0.14)	0.37
MS/BS (%)	1.64 (0.82, 2.94)	0.61 (0.39, 1.29)	0.87 (0.60, 1.89)	6.1
BFR/BV (mm <sup>2</sup> /mm <sup>2</sup> /year)	0.05 (0.04, 0.10)	0.02 (0.01, 0.04)	0.04 (0.02, 0.08)	0.19
Tabular bone micro-architecture and structure				
Tb.Th (µm)	146.5 (134, 163)	149.0 (131, 180)	138.0 (128, 155)	128
Tb.N (%)	1.34 (1.26, 1.42)	1.30 (1.15, 1.48)	1.30 (1.28, 1.42)	1.67
Tb.Sp (µm)	732.5 (688.0, 792.0)	748.0 (695.0, 861.0)	753.5 (689.0, 771.0)	587

## CONCLUSIONS

- In postmenopausal women with osteoporosis, 2mg q2mo and 3mg q3mo i.v. ibandronate injections (providing an annual cumulative exposure of 12mg) have a bone safety profile that is generally comparable to the daily oral regimen; no adverse effects on the quality of newly formed bone were detected and no impairment of bone mineralization was observed.
- This finding is noteworthy, since the annual cumulative exposure to ibandronate provided by the i.v. regimens is the highest tested to date in osteoporotic women.

## REFERENCES

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