

Progressive efficacy improvements with quarterly intravenous ibandronate injections: the DIVA study long term extension

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SUMMARY

- The Dosing IntraVenous Administration (DIVA) study evaluated bone mineral density (BMD) in women with postmenopausal osteoporosis receiving intravenous (i.v.) ibandronate (Bonviva®) [2mg every 2 months (q2mo) or 3mg every 3 months (q3mo)].^{1,2}
- i.v. ibandronate was associated with superior efficacy to an established daily oral ibandronate regimen (2.5mg)³ for gains in lumbar spine BMD (p<0.001).^{1,2}
- The efficacy and tolerability of i.v. ibandronate are being investigated in a 3-year extension of the DIVA study. Patients from participating centres either continued to receive their i.v. ibandronate regimen or were re-randomised from daily oral ibandronate.
- Data from the first year of the open-label, long-term extension (LTE) study have been analysed and a post-hoc pooled analysis conducted on patients who received i.v. ibandronate throughout the 3 years of the DIVA study plus the LTE.
- Mean gains in BMD above the increases reported at the end of DIVA were seen for lumbar spine (0.92% and 0.95%) and total hip (0.48% and 0.13%) for 2mg and 3mg, respectively.
- The post-hoc, pooled analysis at 3 years showed consistent BMD increases that were significant for lumbar spine (7.6% and 7.0% in the 2mg and 3mg groups, respectively) and proximal femur (3.7% and 3.3% in the 2mg and 3mg groups, respectively) when compared to the original DIVA baseline levels (p<0.0001).
- Reductions in serum CTX were maintained from the end of DIVA; median increases in trough levels at month 12 were 18.3% (2mg q2mo) and 9.81% (3mg q3mo), and median reductions in peak levels at month 6 of the extension were 81.7% (2mg q2mo) and 85.7% (3mg q3mo).
- In conclusion, 1-year data from the DIVA study LTE demonstrated that i.v. ibandronate continued to build on increases in lumbar spine and proximal femur BMD that were observed in DIVA, and the substantial reductions in bone turnover seen in DIVA were maintained.

INTRODUCTION

- Ibandronate is a potent, nitrogen-containing bisphosphonate used for the treatment of postmenopausal osteoporosis.
- The efficacy of oral ibandronate has been demonstrated in a number of clinical trials.³⁻⁵
- However, oral bisphosphonate therapy is not appropriate for all patients, and an i.v. formulation has been developed that is associated with dose-dependent, clinically meaningful increases in BMD and reductions in markers of bone turnover when administered at 3-monthly intervals.^{7,8}
- To define the optimal dosing regimen for i.v. ibandronate, the DIVA study was initiated.^{1,2}
 - i.v. ibandronate regimens of 2mg q2mo and 3mg q3mo were compared with a daily oral ibandronate regimen of proven antifracture efficacy (2.5mg; vertebral fracture risk reduction: 62%, p=0.001).³
- Bone turnover and BMD are key components of bone strength. In DIVA, i.v. ibandronate was associated with significantly greater increases in lumbar spine BMD compared with the oral regimen (2mg q2mo, 6.4% and 3mg q3mo, 6.3% vs 4.8%; p<0.001).² BMD gains are associated with fracture risk reduction.⁹⁻¹¹
- Here, we present efficacy data from patients who completed 2 years of treatment in the DIVA study and subsequently entered the DIVA study LTE.

METHODS

Study design

- Open-label extension to a randomised, double-blind, double-dummy, phase III, non-inferiority study in women aged 55–80 years with postmenopausal (≥5 years since menopause) osteoporosis (mean lumbar spine [L2–L4] BMD T-score <–2.5 and ≥–5.0).
- In the original study, patients received i.v. ibandronate injection (2mg q2mo or 3mg q3mo) or daily oral ibandronate (2.5mg) for 2 years.

- Those completing 2 years of treatment, and who were ≥75% compliant with treatment in the last year of the DIVA study, were eligible for the DIVA study LTE
 - patients previously receiving i.v. ibandronate injection continued on the same regimen for an additional 3 years
 - those who received oral ibandronate were randomised to one of the two i.v. ibandronate regimens at the start of the DIVA study LTE.
- All patients received daily calcium (500mg) and vitamin D (400IU).

Study endpoints

- Efficacy endpoints in the DIVA study LTE included
 - relative change (%) in mean lumbar spine (L2–L4) BMD from baseline to month 12
 - relative change (%) in trochanter, femoral neck and total hip BMD from baseline to month 12.
- In a subgroup of patients, relative change (%) from baseline in serum CTX at trough and peak suppression (steady state) was evaluated.
- In a post-hoc analysis, data were pooled from all patients who received i.v. ibandronate continuously for 3 years in DIVA and the DIVA study LTE.

Analysis populations

- The primary efficacy analysis population for the 1- and 3-year analyses is the intent-to-treat (ITT) population
 - defined as all patients who received at least one dose of study medication and had at least one follow-up data point
 - data previously published from DIVA 1 and 2 years are for the per protocol population and as such the data are not directly comparable.^{1,2}

RESULTS

Patient characteristics

- Of 1,386 patients who received ibandronate in DIVA, 781 were enrolled into the DIVA study LTE. The ITT population consisted of 758 of these patients: 2mg q2mo n=365; 3mg q3mo n=393.
- The number of patients entering the DIVA study LTE is lower than those completing the original DIVA study, as 26 of the 58 centres from DIVA participated in the DIVA study LTE.
- Patient characteristics for the ITT population were well balanced across the two treatment arms (Table 1).

Table 1 Baseline patient demographics DIVA study LTE (ITT population, mean).

	i.v. ibandronate	
	2mg q2mo (n=365)	3mg q3mo (n=393)
Age (years)	68.1	67.9
Weight (kg)	64.3	64.9
Lumbar spine (L2–L4) BMD (g/cm ²)	0.80	0.79
Lumbar spine (L2–L4) BMD (T-score)	–2.84	–2.90
Serum CTX (ng/mL)*	0.22	0.25

*Median; †2mg q2mo n=117, 3mg q3mo n=119

Bone mineral density

- During the first year of treatment in the DIVA study LTE, mean lumbar spine BMD increased significantly relative to the values recorded at the end of the 2-year DIVA study (Table 2).
- Increases in BMD were also observed at the femoral neck, trochanter and total hip (Table 2).

Table 2 Relative change (%) in mean (95% confidence interval [CI]) BMD from DIVA study LTE baseline to month 12.

	i.v. ibandronate	
	2mg q2mo (n=365)	3mg q3mo (n=393)
Lumbar spine	0.92 (0.59, 1.26)**	0.95 (0.59, 1.31)**
Total hip	0.48 (0.21, 0.74)**	0.13 (–0.17, 0.44)*
Femoral neck	0.73 (0.34, 1.12)**	0.30 (–0.09, 0.70)*
Trochanter	0.86 (0.51, 1.22)**	0.62 (0.20, 1.03)**

**p<0.05 based on the 95% CI; *p=354; †n=387; ‡n=351; §n=382

- In patients who received i.v. ibandronate continuously for 3 years, lumbar spine BMD increased significantly from the original baseline of DIVA, by 7.6% and 7.0% in the 2mg and 3mg group, respectively (p<0.0001 for both; Figure 1).

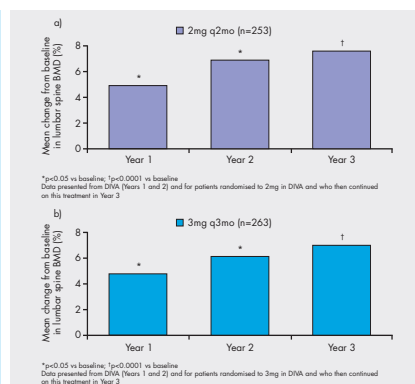


Figure 1 Mean relative change (%) from baseline in lumbar spine BMD with 3 years' continuous treatment with a) i.v. ibandronate 2mg q2mo and b) 3mg q3mo (ITT population; combined BMD analysis).

- Proximal femur BMD also increased significantly at 3 years in those patients who continued taking i.v. ibandronate 2mg q2mo or 3mg q3mo (p<0.0001; Figure 2).

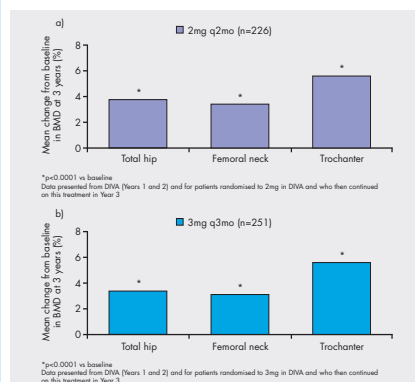


Figure 2 Mean relative change (%) from baseline in proximal femur BMD with 3 years' continuous treatment with a) i.v. ibandronate 2mg q2mo and b) 3mg q3mo (ITT population; combined BMD analysis).

Bone turnover

- The bone turnover analysis included 117 patients in the 2mg q2mo group and 119 patients in the 3mg q3mo group. Relative to the DIVA study baseline
 - median trough CTX levels at month 36 were decreased by 40.2% and 41.4% in the 2mg q2mo and 3mg q3mo groups, respectively (p<0.0001 for both)
 - median peak serum CTX levels at month 30 were decreased by 89.0% and 92.4% in the 2mg q2mo and 3mg q3mo groups, respectively (p<0.0001 for both).

CONCLUSIONS

- In DIVA, 1 and 2 years of treatment with i.v. ibandronate (3mg q3mo) resulted in strong BMD increases at the lumbar spine and proximal femur.^{1,2}
- Patients who received an additional year of i.v. ibandronate in the DIVA study LTE had further increases in lumbar spine and proximal femur BMD.
- In patients who received i.v. ibandronate continuously for 3 years, lumbar spine and proximal femur BMD increased progressively.
- The substantial reductions in bone turnover seen in DIVA were maintained after an additional year of therapy.
- These data show that i.v. ibandronate (3mg q3mo) provides a consistent effect on two of the main components of bone strength, bone turnover and BMD, in women with postmenopausal osteoporosis.

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