

Intermittent intravenous ibandronate injections are more effective than an established daily oral regimen: DIVA 2-year results

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SUMMARY

- Oral bisphosphonates are the current standard of care for women with postmenopausal osteoporosis.
- However, oral dosing may be contraindicated or unsuitable for some patients, including women with gastrointestinal (GI) intolerance, those who cannot comply with the requisite procedures for oral dosing or who are receiving several concomitant oral medications. An effective and well-tolerated intravenous (i.v.) bisphosphonate may be an attractive treatment option for these patients.
- Ibandronate (Bonviva[®]) is a potent, nitrogen-containing bisphosphonate, with proven efficacy (vertebral fracture risk reduction 62%, p=0.0001) and a tolerability profile similar to placebo, when administered orally.¹
- Ibandronate can also be administered as a short (15–30 seconds) i.v. injection with extended dosing intervals. The Dosing IntraVenous Administration (DIVA) study demonstrated after 1st and 2 years, superior lumbar spine bone mineral density (BMD) gains with 2mg every 2 months (q2mo) or 3mg every 3 months (q3mo) i.v. ibandronate injections compared with daily oral dosing – both i.v. regimens were statistically superior to the daily oral regimen (p<0.001) – compared with the daily oral regimen, consistently greater increases in proximal femur BMD were also obtained in the i.v. groups (p<0.001, total hip and trochanter).
- In all treatment arms, reductions in serum CTX (sCTX) concentrations were observed throughout the study.
- In general, the overall adverse event profile of the intermittent i.v. ibandronate regimens was similar to that of the daily oral regimen after 2 years.
- The favourable tolerability profile, combined with the BMD gains, suggest that intermittent i.v. ibandronate injections provide a beneficial therapy for patients with postmenopausal osteoporosis who are unable to use oral bisphosphonates.

INTRODUCTION

- Oral bisphosphonates are the current standard of care for postmenopausal osteoporosis; however, oral dosing may be contraindicated or unsuitable for some patients, including those who have GI intolerance, cannot comply with the requisite procedures for oral dosing (fasting and posture) or are receiving several concomitant oral medications.
- An effective and well-tolerated i.v. bisphosphonate could provide a treatment possibility for these patients, whose postmenopausal osteoporosis may not be adequately managed.
- Ibandronate is a potent, nitrogen-containing bisphosphonate. Administered orally, it has proven vertebral fracture efficacy (62% risk reduction, p=0.0001) and a tolerability profile similar to placebo.¹
- Ibandronate can also be administered as a short (15–30 seconds) i.v. injection with extended dosing intervals.
- The DIVA study was designed to identify the optimal i.v. ibandronate injection dosing schedule by comparing the efficacy and safety of 2mg q2mo or 3mg q3mo ibandronate i.v. injections with the proven daily oral ibandronate regimen (2.5mg in women with postmenopausal osteoporosis).
- The 1-year findings demonstrated that both i.v. regimens were statistically non-inferior to the daily oral regimen in increasing lumbar spine BMD² – moreover, both regimens were demonstrated to be statistically superior to the daily oral regimen (p<0.001) and achieved substantial reductions in sCTX.
- Results of the 2-year analysis, undertaken to corroborate the findings of the 1-year efficacy analysis and to provide more extensive safety and tolerability information for the i.v. regimens, are presented here.

METHODS

Study design and participants

- DIVA was a multicentre, randomised, double-blind, double-dummy, phase III, non-inferiority study (Figure 1).

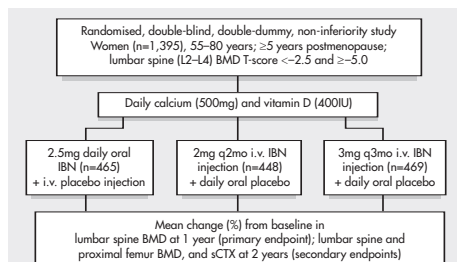


Figure 1. DIVA study design.

Study endpoints

- The primary efficacy endpoint was mean change (%) from baseline in lumbar spine (L2–L4) BMD after 1 year.
- Secondary endpoints at 2 years included – the mean change (%) from baseline in lumbar spine (L2–L4) and proximal femur BMD – the proportion of patients (%) defined as responders, that is, those patients with an increase in BMD ≥ baseline, and the proportion achieving increases in lumbar spine or total hip BMD previously associated with antifracture efficacy, i.e. ≥6% and ≥3%, respectively – the change (%) from baseline in sCTX, a biochemical marker of bone resorption, at 2, 4, 6, 12 and 24 months (2mg q2mo) or 3, 6, 12 and 24 months (3mg q3mo).
- Adverse events were continuously monitored throughout the study.

Statistical analysis

- The per-protocol (PP) population was used for the primary analysis of efficacy endpoints, in line with international clinical guidelines³ – confirmatory analyses were conducted using the intent-to-treat (ITT) population.
- At 2 years, the changes (%) from baseline in lumbar spine BMD with the i.v. injection regimens were compared with the oral regimen, using a non-inferiority test – non-inferiority would be concluded if the lower bound of the one-sided 97.5% CI for the difference in means between the i.v. regimens and the oral daily regimen was ≥–1.3%, i.e. 30% of the minimum treatment difference observed previously between daily oral ibandronate and placebo³ – in the event of non-inferiority, superiority of the i.v. regimens to the daily regimen would be tested using ANOVA.

RESULTS

Patient disposition and baseline characteristics

- In total, 1,395 osteoporotic women were randomised. Patient characteristics were well-balanced across all three groups at baseline (Table 1).

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

	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
Time since menopause (years)	18.1	19.2	18.2*
Lumbar spine (L2–L4) BMD (T-score)	–3.26	–3.28	–3.29*
Prevalent fracture (%)	44.4	41.8	42.9

*n=363

Efficacy

- After 2 years, similar increases from baseline in lumbar spine BMD were obtained, with the q2mo (6.4% [95% CI: 5.9, 6.9]) and q3mo (6.3% [95% CI: 5.7, 6.8]) regimens (Figure 2) – both i.v. dosing regimens were statistically non-inferior and, in fact, superior (p<0.001) to the daily oral regimen for lumbar spine BMD increases (4.8% [95% CI: 4.3, 5.4]).
- Compared with the daily oral regimen, consistently greater increases were obtained in proximal femur BMD in the i.v. groups (Figure 2) – total hip and trochanter BMD gains were statistically superior to the daily group (post-hoc analysis: p<0.001 for all comparisons).

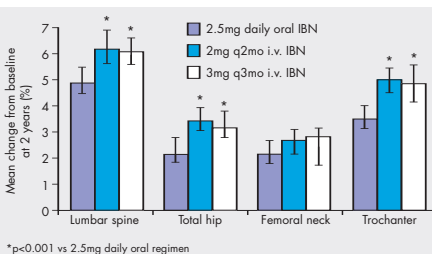


Figure 2. Significant lumbar spine BMD increases and increases in proximal femur BMD with i.v. ibandronate injection versus the daily oral regimen (PP population).

- The results of the ITT analysis confirmed the PP analysis.
- After 2 years, significantly more patients in the i.v. arms than the daily arm achieved increases in – lumbar spine BMD above baseline (92.8% in both i.v. arms vs 84.7%; p=0.001) and ≥6% (53.1% and 49.4% in the q2mo and q3mo arms, respectively, vs 37.7%; p<0.002 for both comparisons)

- total hip BMD above baseline (88.6% and 85.6%, respectively, vs 77.0%; p<0.004 for both comparisons) and ≥3% (56.3% and 49.8%, respectively, vs 40.3%; p<0.014 for both comparisons).
- In all treatment arms, pronounced and clinically meaningful reductions in sCTX concentrations were observed and maintained throughout the study (at 2 years: 53.4–59.9%; Table 2).

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

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

Safety and tolerability

- A similar incidence of adverse events was observed in the daily oral and i.v. groups (Table 3).

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

	2.5mg daily oral IBN (n=465)	2mg q2mo i.v. IBN (n=448)	3mg q3mo i.v. IBN (n=469)
Overall			
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	2 (0.4)	3 (0.7)	0 (0)
Death, n (%)	4 (<1)	3 (<1)	2 (<1)

*Excluding flu-like symptoms

- Despite a comparable incidence of adverse events leading to withdrawal from the study across the treatment groups, a higher overall incidence of drug-related adverse events was reported in the i.v. treatment groups than in the daily oral treatment group (Table 3).
- In general, this imbalance was caused by a higher incidence of symptoms commonly associated with i.v. bisphosphonate administration, namely transient musculoskeletal symptoms (e.g. myalgia and arthralgia) and flu-like illness.

Flu-like illness

- Flu-like illness, a combination of the investigator-reported adverse event terms 'influenza-like illness' and 'acute-phase reaction', was observed in the i.v. groups (5.6% in the 2mg q2mo and 4.9% in the 3mg q3mo groups vs 1.5% with daily) – symptoms were generally mild-to-moderate in intensity and caused few withdrawals (1.1%, 2.8% and 0.4%, respectively).
- The adverse event numbers are cumulative over the 2 years of the study; however, 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.

Renal safety

- Over the entire 2-year treatment period, the proportion of patients with adverse events attributable to renal and urinary disorders was low and similar in all three treatment groups (4.5% and 3.2% for 2mg q2mo and 3mg q3mo arms, respectively, compared with 3.9% in the daily oral group). There were no reports of acute renal failure with any regimen.

CONCLUSIONS

- This study found that in women with postmenopausal osteoporosis ibandronate i.v. injections (2mg q2mo or 3mg q3mo) are – statistically superior in terms of increasing lumbar spine, total hip and trochanter BMD to the established daily oral ibandronate regimen – well tolerated with an overall adverse event profile comparable with daily oral ibandronate and good renal tolerability.
- I.v. administration of ibandronate offers an effective, alternative treatment option for patients who cannot tolerate oral bisphosphonates or cannot comply with the strict dosing guidelines.

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