

Oral weekly ibandronate prevents bone loss in postmenopausal women

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SUMMARY

- Ibandronate (Boniva[®]) is a potent nitrogen-containing bisphosphonate that can be administered intermittently. Oral ibandronate provides highly significant fracture reduction when administered with a between-dose interval of 9–10 weeks, in the treatment of postmenopausal osteoporosis (PMO).
- This multicenter, double-blind, placebo-controlled phase II/III study investigated the efficacy, safety and optimal dose of oral weekly ibandronate in the prevention of bone loss in 630 postmenopausal women stratified according to initial bone mass and time since menopause (TSM), as shown in **Table 1**.
- Patients received calcium supplementation plus oral weekly ibandronate 5mg (n=159), 10mg (n=154) or 20mg (n=159) or placebo (n=158) for 2 years.
- After 2 years, oral weekly ibandronate produced a dose-related and consistent increase in bone mineral density (BMD) at the lumbar spine (L1–L4) and hip (total hip, femoral neck and trochanter), relative to baseline
 - greatest increases in lumbar spine BMD were seen with the 20mg dose in osteopenic women with >3 years since menopause onset.
- BMD increases correlated with dose-dependent and sustained reductions in biochemical markers of bone turnover.
- Once weekly dosing of oral ibandronate (20mg) is effective and well-tolerated for preventing bone loss in postmenopausal women.

INTRODUCTION

- Intermittent dosing of ibandronate, a potent nitrogen-containing bisphosphonate, has been shown to evoke significant increases in bone mass and provide pronounced fracture reduction in osteoporotic women.¹
- However, the efficacy of an oral weekly ibandronate regimen in the prevention of early and late postmenopausal bone loss, in healthy and osteopenic women, has not yet been demonstrated.
- Due to poor bioavailability and gastrointestinal (GI) safety concerns, oral bisphosphonate dosing is currently associated with stringent dosing requirements (e.g. post-dose fasts, posture requirements)^{2–4}
 - these limitations may potentially reduce compliance, hence jeopardizing therapeutic outcomes.
- Less frequent dosing may help overcome these limitations
 - less frequent dosing schedules are predicted to promote long-term therapy adherence and optimize patient management in osteoporosis
 - a recent study showed that 9/10 patients prefer weekly to daily bisphosphonate dosing⁵
 - less frequent administration is thought to be beneficial in patients with frequent esophageal reflux, as daily exposure to oral bisphosphonates may inhibit the repair of gastric acid-induced injury.⁶
- The objectives of this phase II/III study were to investigate the efficacy, safety and dose response of oral weekly ibandronate in the prevention of bone loss in postmenopausal women.

METHODS

Study design

- Multicenter, placebo-controlled, double-blind, randomized, 2-year phase II/III dose-finding study.
- Written informed consent was obtained from all patients.

Study population

- 630 postmenopausal women (1–10 years since last menstruation) were enrolled into one of four strata based on TSM and baseline lumbar spine BMD (**Table 1**).

Table 1. Enrollment strata.

	Normal BMD	Osteopenic (lumbar spine BMD T-score <-1)
Early PM (1–3 years)	Stratum A n=105	Stratum B n=200
Later PM (>3 years)	Stratum C n=107	Stratum D n=218

Dosing regimen

- Patients were randomized to receive either oral weekly ibandronate, 5mg (n=159), 10mg (n=154) or 20mg (n=159), or placebo (n=158) for 2 years
 - patients were instructed not to take any food for at least 6 hours prior to, and for at least 30 minutes after, study medication
 - all participants received daily calcium supplementation (500mg daily).

Study endpoints

- Primary endpoint: mean relative change from baseline in BMD of the lumbar spine (L1–L4) after 2 years.
- Secondary endpoints
 - absolute and relative change in BMD at the proximal femur (total hip, femoral neck and trochanter)
 - change from baseline in rate of bone turnover (serum C-telopeptide [CTX] and urinary CTX, serum osteocalcin, serum bone-specific alkaline phosphatase and serum parathyroid hormone [PTH]).
- Safety endpoints: adverse events, parameters of renal and liver function, other laboratory parameters (including blood counts and serum electrolyte concentrations).

RESULTS

- Baseline demographics were balanced across the four treatment groups in terms of age, weight, TSM, BMD, biochemical markers of bone turnover, vitamin D levels, patient medical background, physical activity and diet.

Efficacy

BMD at the lumbar spine

- All strata: both the 10mg and 20mg doses statistically significantly increased BMD of the lumbar spine, compared with placebo (**Figure 1**)

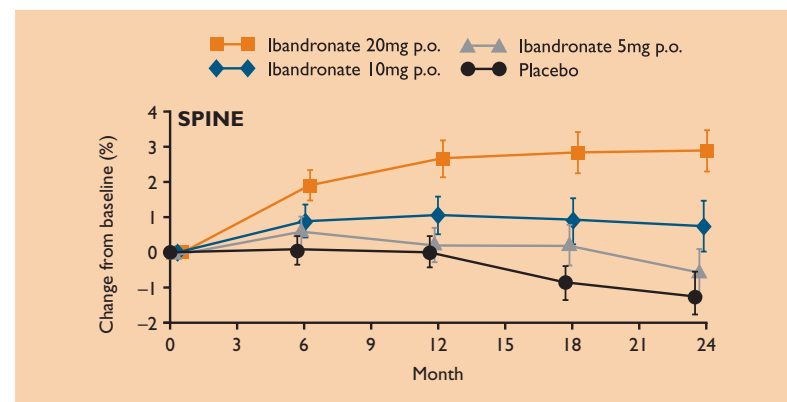


Figure 1. Mean relative change from baseline in lumbar spine BMD in the intent-to-treat (ITT) population.

- significant differences were demonstrated at all time points, beginning at month 6 for the 10mg and 20mg dose groups (the mean relative change in BMD of lumbar spine was not significantly different from placebo in the 5mg dose group).

BMD of the lumbar spine by stratum

- ibandronate groups improved mean relative change in spine BMD at month 24 in all four strata versus their respective placebo groups, with one exception (stratum A, 5mg group)
- stratum A: spinal BMD changes from baseline at 2 years
 - approximately 2.0%, -0.2%, -2.6% and -2.3% for the 20mg, 10mg, 5mg and placebo groups, respectively
- stratum B: spinal BMD changes from baseline at 2 years
 - approximately 3%, -0.1%, -1.4% and 2.3% for the 20mg, 10mg, 5mg and placebo groups, respectively
- stratum C: spinal BMD changes from baseline at 2 years
 - approximately 2.1%, 1.1%, 0.3% and -0.3% for the 20mg, 10mg, 5mg and placebo groups, respectively
- stratum D: spinal BMD changes from baseline at 2 years
 - the greatest difference in mean relative change of spine BMD between placebo and ibandronate was seen in stratum D
 - approximately 3.6%, 1.7%, 0.8% and 0.1% for the 20mg, 10mg, 5mg and placebo groups, respectively.

BMD at the hip

- All strata: all active drug groups displayed dose-dependent increases in BMD changes at the total hip, femoral neck and trochanter (**Figure 2**)
- relative changes from baseline to month 24 between the 10mg and 20mg group compared with placebo were significant for total hip and its sub-regions.
- BMD of total hip and its sub-regions by stratum
 - patients of strata C and D (>3 years TSM) showed a trend toward a greater treatment effect with oral ibandronate after 2 years than patients in strata A and B (TSM 1–3 years).

Biochemical markers of bone turnover

- Urinary CTX levels: all doses of ibandronate produced a consistent, dose-dependent decrease in urinary CTX levels throughout the course of the study (**Figure 3**)
- Serum CTX levels: reduced from baseline in a dose-dependent fashion with 10mg and 20mg ibandronate
 - 20mg ibandronate consistently suppressed serum CTX by approximately 38% from baseline. The decrease in serum CTX values observed with 20mg ibandronate differed significantly from placebo at all time points.
- Serum osteocalcin levels: 10mg and 20mg ibandronate groups showed significant, dose-dependent reductions from baseline in serum osteocalcin levels, as compared with placebo, beyond month 3 (**Figure 4**).
- Alkaline phosphatase levels: showed significant decrease beyond month 3 for the 20mg dose group versus placebo.
- PTH levels: showed small, clinically insignificant, changes from baseline.

Safety

- Overall safety results indicated that oral weekly treatment with ibandronate was well tolerated at the three doses investigated and the safety profile was similar to placebo, with no safety concerns identified.
- The percentages of patients who experienced adverse events, adverse events related to treatment, serious adverse events and withdrew from treatment due to adverse events were balanced across the three ibandronate treatment groups and were not significantly different from those seen with placebo.

- No serious adverse events were assessed as related to study medication.

- The proportion of patients experiencing >1 drug-related adverse event was low (7.2%); the 5mg and 10mg groups had twice the number of patients experiencing drug-related adverse events compared with the placebo and 20mg group
 - although GI system adverse events were the most frequent drug-related events, they only occurred in 3%, 6%, 5% and 3% of patients receiving placebo or 5mg, 10mg and 20mg ibandronate, respectively.

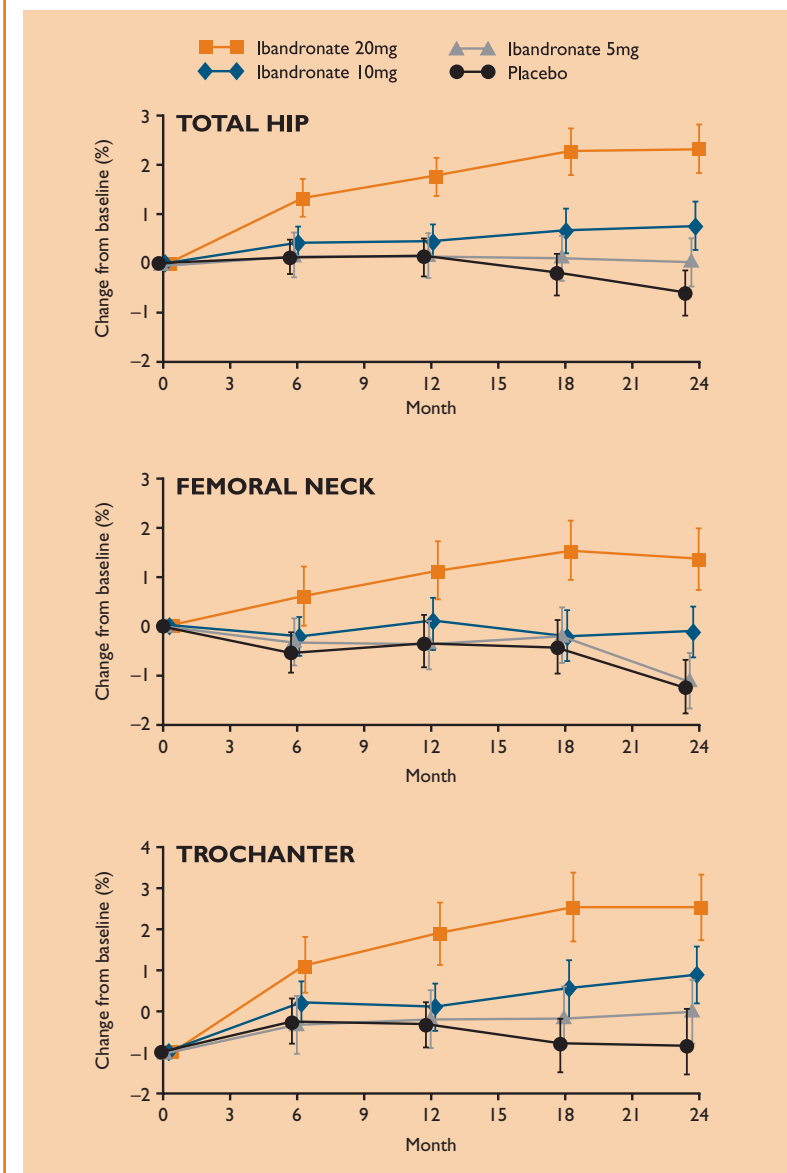


Figure 2. Mean relative BMD change from baseline at the total hip, femoral neck and trochanter in the ITT population.

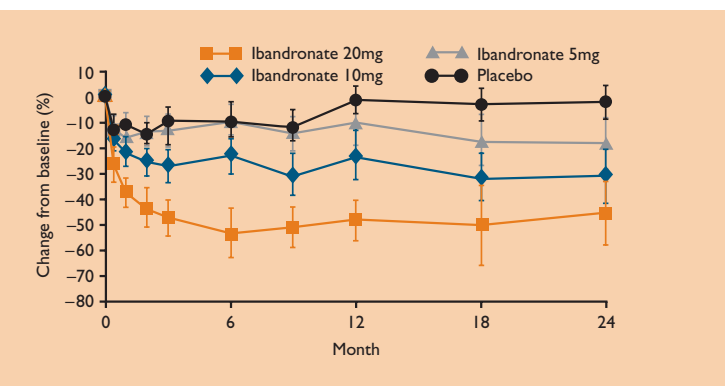


Figure 3. Median relative change in urinary CTX from baseline in the ITT population.

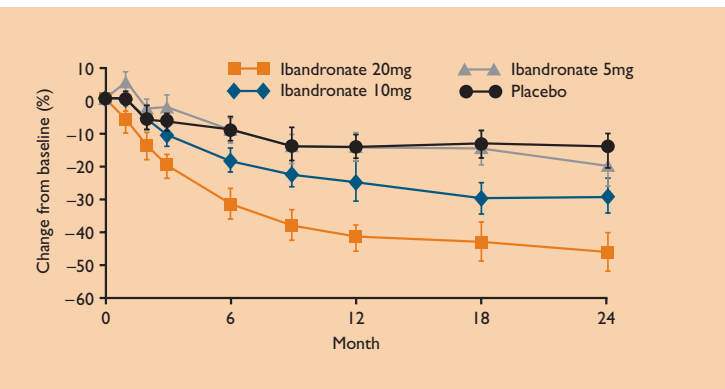


Figure 4. Median relative change in serum osteocalcin from baseline in the ITT population.

CONCLUSIONS

- Two-year treatment with oral weekly ibandronate produced dose-dependent increases in BMD at the lumbar spine and total hip, relative to placebo, with a significant difference from placebo observed with both the 10mg and 20mg doses.
- These effects were seen in early postmenopausal osteopenic women but were more pronounced in osteopenic women of >3 years menopausal.
- The BMD increases correlated with dose-dependent and sustained reductions in bone turnover markers (greatest difference from placebo seen with the 20mg dose).
- Overall safety results indicated that oral weekly ibandronate is well tolerated.
- Other trials of more convenient ibandronate regimens are ongoing.

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