

# Weekly dosing of oral ibandronate is effective in the prevention of bone loss in postmenopausal osteoporosis

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## SUMMARY

- Ibandronate 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 (PM) osteoporosis.
- This multicentre, 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 PM women.
- 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.
- Oral weekly ibandronate holds promise as an effective, well-tolerated and convenient alternative to oral daily bisphosphonates for the prevention of bone loss in PM women.

## INTRODUCTION

- Oral bisphosphonates are important therapeutics for the prevention of bone loss in PM women.
- However, 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)<sup>1–3</sup>
  - these limitations may potentially reduce compliance, hence jeopardising therapeutic outcomes.
- Weekly dosing may help overcome these limitations
  - less frequent dosing schedules are predicted to promote long-term therapy adherence and optimise patient management in osteoporosis
  - a recent study showed that 9/10 patients prefer weekly to daily bisphosphonate dosing<sup>4</sup>
  - in the case of alendronate, less frequent administration is thought to be beneficial in patients with frequent oesophageal reflux, as daily exposure to oral bisphosphonates may inhibit the repair of gastric acid-induced injury.<sup>5</sup>
- Oral ibandronate, a potent nitrogen-containing bisphosphonate, has been shown to provide highly significant fracture reduction when administered with a between-dose interval of 9–10 weeks, in treatment of PM osteoporosis.<sup>6</sup>
- 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 PM women.

## METHODS

### Study design

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

### Study population

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

Table 1. Enrolment 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 randomised 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 (AEs), 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)
  - 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.

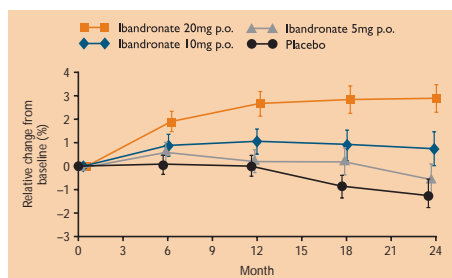


Figure 1. Mean relative change from baseline in lumbar spine BMD in the intent-to-treat [ITT] population.

#### 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 change 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

- 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.
- Urinary CTX levels: all doses of ibandronate produced a consistent, dose-dependent decrease in urinary CTX levels throughout the course of the study
  - the decrease in median urinary CTX values mirrored that of serum CTX.
- Osteocalcin levels: 10mg and 20mg ibandronate groups showed significant, dose-dependent reductions from baseline in osteocalcin levels, as compared with placebo, beyond month 3.
- Alkaline phosphatase levels: showed significant decrease beyond month 3 for the 20mg dose group versus placebo.
- PTH levels: showed small changes from baseline.

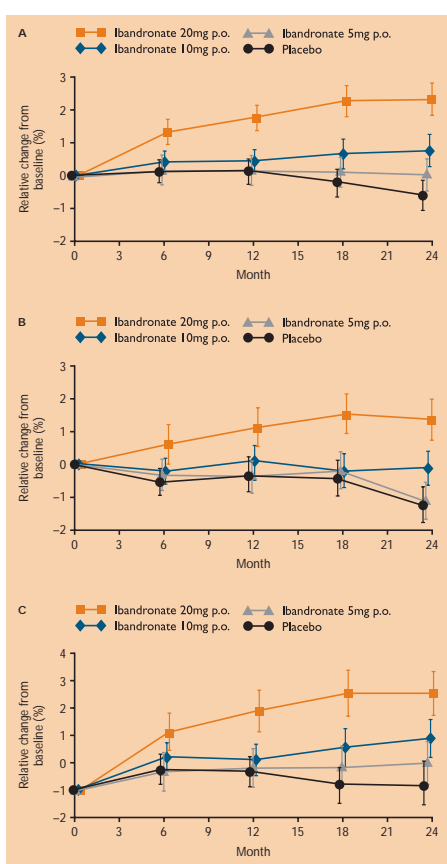


Figure 2. Mean relative BMD change from baseline at the total hip (a), femoral neck (b) and trochanter (c) in the ITT population.

### 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 AEs, AEs related to treatment, serious AEs and withdrew from treatment due to AEs were balanced across the three ibandronate treatment groups and were not significantly different from those seen with placebo.
- No serious AEs were assessed as related to study medication.
- The proportion of patients experiencing >1 drug-related AE was low (7.2%); the 5mg and 10mg groups had twice the number of patients experiencing drug-related AEs compared with the placebo and 20mg group
  - although digestive system AEs 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.

## 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 PM 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).
- Thus, it appears that 20mg is the most efficacious dose of oral weekly ibandronate in preventing bone loss.
- Overall safety results indicated that oral weekly treatment with ibandronate is well tolerated.
- In summary, oral weekly ibandronate holds promise as an effective, well-tolerated and convenient alternative to oral daily bisphosphonates and HRT in the prevention of bone loss in PM women.
- Other trials of oral ibandronate are ongoing/planned.

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