

Upper gastrointestinal safety and tolerability profile of once-monthly and daily oral ibandronate: MOBILE 2-year analysis

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SUMMARY

- In the oral ibandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE), an overall adverse event and upper gastrointestinal (GI) tolerability profile similar to placebo was observed with a daily oral ibandronate (Bonviva®) (2.5mg) regimen.¹
- In the Monthly Oral ibandronate In LadiEs (MOBILE) study, monthly oral dosing of ibandronate (50+50mg, 100mg or 150mg) was at least as effective and similarly well-tolerated as the efficacious daily oral regimen (2.5mg; 3-year vertebral fracture risk reduction: 62%) in 1,609 women with postmenopausal osteoporosis.²
- After 2 years, the overall incidence of upper GI adverse events was similar across the treatment groups (19.9–25.8%).
- With the exception of the 150mg group, in which the incidence was markedly lower (27.1%), the incidence of upper GI adverse events in patients with a history of upper GI disorder was similar in the monthly and the daily arms (45.2–48.9%).
- The incidence of upper GI events in patients who received concomitant non-steroidal anti-inflammatory drugs (NSAIDs) was similar across the treatment groups (23.6–31.2%).
- In patients who took concomitant anti-peptic agents (proton pump inhibitors [PPIs] or H₂ antagonists), upper GI adverse events were more frequent overall, but the monthly regimens were again as well tolerated as the daily regimen (53.8–66.7%).
- Despite administration of relatively higher single doses, monthly oral ibandronate has a similar upper GI safety profile to the established daily dosing regimen in women with postmenopausal osteoporosis, even in those at increased risk for such events.

- In the MOBILE study, monthly oral ibandronate regimens (50+50mg, 100mg or 150mg) were at least as effective and similarly well tolerated as the daily regimen (2.5mg) over 2 years of treatment,² despite the administration of relatively higher single doses (100–150mg).
- Upper GI tolerability was also prospectively evaluated. Over 1 year of treatment, monthly oral ibandronate was found to have a similar upper GI tolerability profile to the daily oral regimen.
- The daily oral regimen is known to have an upper GI tolerability profile similar to placebo, even in patients at increased risk for such events.
- Here, an analysis of upper GI adverse events after 2 years of treatment with monthly oral ibandronate is presented.

METHODS

Study design

- This was a multinational, randomised, double-blind, phase III, non-inferiority study.
- Eligible women were aged 55–80 years, with postmenopausal osteoporosis (≥5 years postmenopause, lumbar spine [L2–L4] bone mineral density [BMD] T-score <–2.5 and ≥–5).
- Patients with a history of upper GI disorder or those with continuing dyspeptic symptoms controlled with regular medication were eligible for inclusion.
- Patients with uncontrolled, active or recurrent peptic ulcer disease were excluded, as were those with upper GI bleeding in the previous year that required hospital treatment or transfusion.
- Concomitant medications with the potential for upper GI irritation, e.g. NSAIDs, were allowed, as were antisecretory drugs (PPIs or H₂ antagonists) for the treatment of dyspepsia and related symptoms.
- Participants received either monthly oral ibandronate (50+50mg [single doses, consecutive days], 100mg or 150mg [single days]) or daily oral ibandronate (2.5mg) for 2 years.
- Study medication was taken with plain water after an overnight fast (≥6 hours); patients were instructed to stay upright and continue fasting for at least 1 hour after dosing.
- All participants received daily oral calcium (500mg) and vitamin D (400IU).

Safety parameters

- Upper GI adverse events were continuously monitored throughout the study.

Safety analysis

- At 2 years, upper GI tolerability was analysed in the overall study population and in patients with a prior history of upper GI disorder, receiving concomitant NSAIDs or taking anti-peptic drugs.
- The safety analysis involved all patients who received at least one dose of study medication (including those who withdrew prematurely) and had at least one follow-up data point.

RESULTS

Patient characteristics

- A total of 1,609 women were randomised to treatment. Of these, 1,583 were included in the safety analysis (Table 1).
- The baseline characteristics of patients in the safety population were similar across the treatment arms (Table 1).

Table 1. Demographics (mean; safety population; 2-year analysis).

	2.5mg daily (n=395)	50+50mg monthly (n=396)	100mg monthly (n=396)	150mg monthly (n=396)
Age (years)	65.8	66.0	66.2	66.2
Weight (kg)	64.1	64.1	64.0	63.7
Height (cm)	157.1	157.4	157.3	158.0
Body mass index (kg/m ²)	25.9	25.8	25.9	25.5
Time since menopause (years)	18.3	18.7	19.1	18.3
History of previous fractures (%)*	48.9	46.3	45.5	47.0
Lumbar spine (L2–L4) BMD (g/cm ²)	0.755	0.755	0.756	0.754
Lumbar spine (L2–L4) BMD (T-score)	–3.28	–3.28	–3.27	–3.28
Serum CTX (ng/mL) [†]	0.49	0.52	0.51	0.50
25-OH-D (ng/mL)	25.7	24.4	25.1	24.7

*Percentage of patients
[†]Median value

Withdrawals

- The overall number of patients who withdrew from the study due to any GI event was low, and the withdrawal rate across the treatment groups was similar (4.0–4.3% in the monthly groups vs 6.1% with daily).

Upper GI tolerability

- The number of patients who reported at least one upper GI adverse event was similar across the treatment groups (19.9–25.8%; Table 2).

Table 2. Incidence of upper GI adverse events (safety population and in subgroups).

	2.5mg daily (n=395)	50+50mg monthly (n=396)	100mg monthly (n=396)	150mg monthly (n=396)
All patients (%)	90/395 (22.8)	79/396 (19.9)	102/396 (25.8)	89/396 (22.5)
Patients with previous upper GI disorder (%)	19/42 (45.2)	22/45 (48.9)	20/44 (45.5)	13/48 (27.1)
Patients receiving NSAIDs (%)	55/211 (26.1)	53/225 (23.6)	67/215 (31.2)	50/212 (23.6)
Patients receiving anti-peptic drugs (%)	48/78 (61.5)	42/63 (66.7)	46/72 (63.9)	35/65 (53.8)

- The three most commonly reported upper GI adverse events, representing ~70% of all adverse events of this type, were dyspepsia (7.8–10.1%), nausea (5.1–6.6%) and upper abdominal pain (4.5–5.1%; Figure 1).
- As expected, patients with a prior history of upper GI disorder experienced a higher incidence of all upper GI adverse events than those with no prior history (41.3% vs 20.4%).
- In the 11% of patients with prior history, upper GI event incidence was 45.2–48.9% across the treatment groups, with the exception of the 150mg group, in which the incidence was 27.1% (Table 2).
- The incidence of upper GI events in patients receiving concomitant NSAIDs (55%) was, as expected, slightly higher than in the total safety population (26.1% in the daily group and 23.6–31.2% in the monthly groups), but there were no relevant differences between the treatment groups (Table 2).
- In total, 18% of patients took concomitant anti-peptic agents. Upper GI events were again more frequent in these patients (61.5% in the daily group and 53.8–66.7% in the monthly groups), but no relevant differences between the once-monthly and daily treatment groups were observed (Table 2).

- In all subgroups, the lowest incidence of upper GI adverse event was consistently associated with the 150mg monthly dose.
- The incidence of serious upper GI adverse events (0.5–1.3%) and withdrawals as a result of a serious upper GI adverse event (0–0.5%) did not differ between treatment groups.

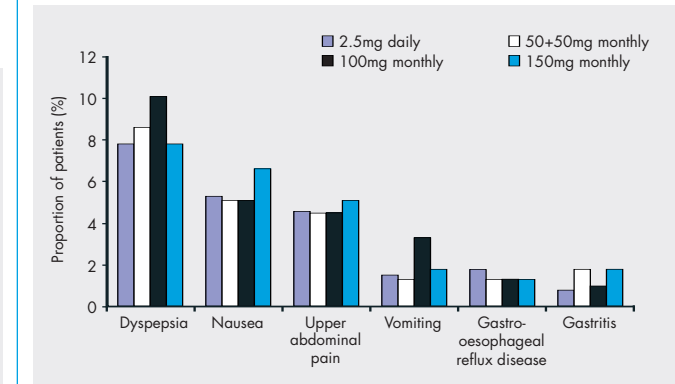


Figure 1. Incidence of dyspepsia, nausea, abdominal pain and other upper GI adverse events (safety population).

CONCLUSIONS

- In postmenopausal osteoporosis, monthly oral ibandronate dosing regimens have a similar upper GI tolerability profile to a daily oral regimen that is known to have an upper GI tolerability profile similar to placebo, even in patients at increased risk for such events.
- Importantly, the increased single doses required for monthly dosing (150mg) did not adversely affect upper GI tolerability.
- These data indicate that monthly oral ibandronate may provide a well tolerated alternative to current daily and weekly oral bisphosphonates in postmenopausal osteoporosis.

REFERENCES

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INTRODUCTION

- Oral bisphosphonates are generally well tolerated, although some patients with postmenopausal osteoporosis experience upper GI adverse events after dosing, which may cause them to prematurely discontinue treatment.³
- Therefore, an effective drug that combines favourable safety and tolerability with a reduced incidence of post-dose upper GI adverse events may improve adherence to treatment regimens.